Tetrahedron: *Asymmetry* 25 (2014) 1275–1279

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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

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ARTICLE INFO

Article history:
Received 25 June 2014
Accepted 19 August 2014
Available online 12 September 2014

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.

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 transformations[6] 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's[15] 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 Bronsted acids[19] or by stepwise formation of the corresponding imidates[20] 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 $ZnCl_2$ 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 ($H_3PW_{12}O_{40}$),[25] cellulose sulfuric acid (CSA),[26] and trichloroisocyanuric acid (TCCA)[27] and more recently, Fe_3O_4 supported Pd(0) nanoparticles (Pd/Fe_3O_4)[28] and $S/Co(NO_3)_2$ 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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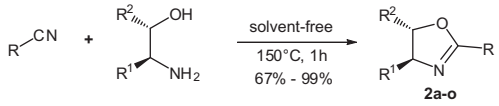
http://dx.doi.org/10.1016/j.tetasy.2014.08.010
0957-4166/

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

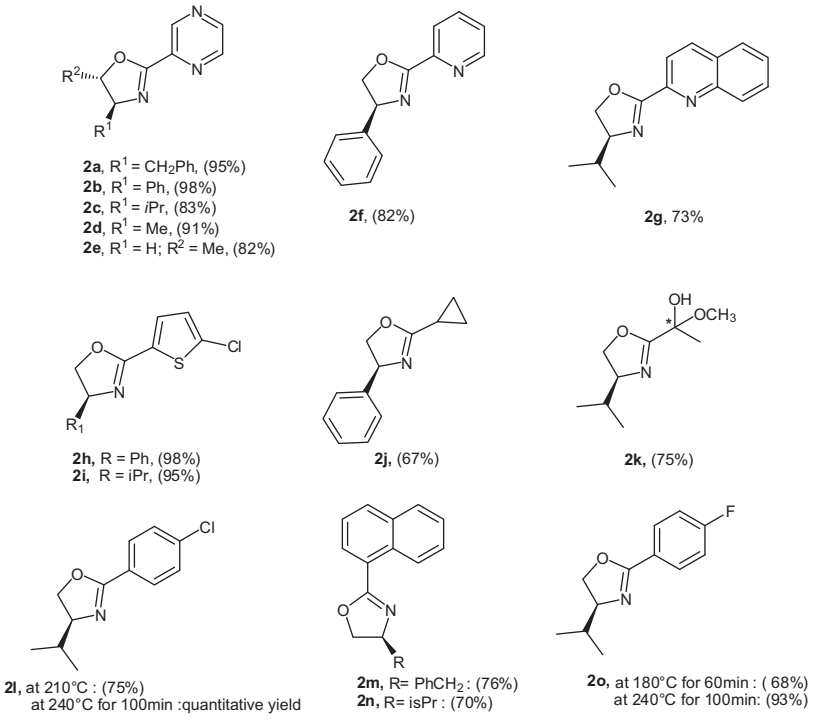
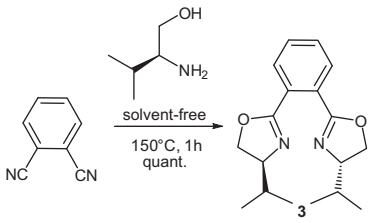


Figure 1. General conditions: nitrile substrate (1 equiv), aminoalcohol (1.1 equiv), solvent-free conditions, MW. 150 °C and 1 h except for oxazolines **2l**, **2m**, **2n**, **2o** that require 240 °C for 100 min.

oxazolines bearing new substituents. The former reacted smoothly with L-valinol affording the unprecedented enantiopure 1-cyclopropyloxazoline **2j** in a fair 67% yield. Surprisingly pyruvonitrile did not afford the expected oxazoline under our reaction conditions. As shown in Figure 1, 1-methoxy-1-[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]ethanol **2k** was obtained in 75% yield. The latter was obtained under classical experimental conditions but required a methanol uptake of the crude material during treatment that plausibly causes the installation of a methoxy moiety at the α-oxazolyl carbon center.[37]

To investigate the effect of the microwave for the condensation of various nitriles, we had originally hoped that the bis-nitrile could be converted into a bis-oxazoline, and we attempted the cyclization reaction with 2.2 equiv of aminoalcohol at 150 °C for 1 h. However, we examined the reaction of the 1,2-dicyanobenzene with the (L)-valinol to afford the 1,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)benzene **3** in quantitative yield under solvent-free conditions at 150 °C for 1 h (Scheme 2).



Scheme 2.

The yield of isolated bis-oxazoline was either higher or comparable to that reported in the literature using solvents and catalytic amounts of various metallic salts.[35] Nevertheless, we aim to test other bisnitriles and to extend this methodology by optimizing the experimental conditions.

3. Conclusion

The reported method proved to be rapid and efficient in converting nitriles into 2-oxazolines in high yields. Unlike some of the previously reported methods, our microwave closed vessel technique requires short reaction times, avoids the use of solvents and of any catalysts. A simple work-up procedure, general applicability, high yields, and mild reaction conditions have made this approach distinctly superior to the many other protocols reported earlier.

4. Experimental

4.1. General comments

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. NMR spectra were recorded on 300 MHz and 200 MHz Bruker spectrometers. Chemical shifts were reported in ppm relative to the residual solvent peak (7.27 ppm for $CHCl_3$) for ^1H spectra and (77.00 ppm for $CDCl_3$) for ^{13}C spectra. High Resolution Mass spectroscopy data were recorded on an Autospec Ultima (Waters/Micromass) device with a resolution of 5000 RP at 5%. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254. The chromatographic analysis was performed on a chiral OJ-H column. A mobile phase of heptane/2-propanol [95:5] was used with a flow rate of 1.0 mL/min at 30 °C. Microwave irradiations were realized using an Anton Paar Monowave 300 apparatus. All of the reactions under microwave irradiation were conducted in a glass vial G4 (TM 0.5–2 mL filling volume, sealed with PTFE-coated silicone septa). Microwave heating was carried out with a single mode cavity Discover Microwave Synthesizer, producing continuous irradiation with IR temperature control. The optimized reaction conditions required heating at 150 °C for 60 min, except for entries **2m**, **n**, **q**, and **o** which required 100 min at 240 °C for oxazoline formation.

4.2. General procedure for the synthesis of the 4-substituted-oxazolines 2a–o

The synthesis of (*S*)-4-phenyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole **2b** is representative.

Pyrazin-2-carbonitrile (15.3 mg, 0.145 mmol, 1 equiv) was mixed with L-(+)-(α)-phenylglycinol (22 mg, 0.160 mmol, 1.1 equiv) in the G4 vial in a Monowave 300 vessel. The resulting mixture was irradiated using the closed vessel mode at 150 °C for 60 min. The reaction mixture was quenched with ethyl acetate and filtered by silica. The filtrate was dried over magnesium sulfate, and concentrated by evaporation under vacuum to give the corresponding (S)-4-phenyl-2-(pyrazin-2-yl)-2-oxazoline **2b** (32.2 mg, 0.143 mmol, 98% yield, entry 2b).

4.2.1. (*S*)-4-Phenyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole 2b

98%; Yellow oil; $[\alpha]_D = -43.5 \pm 2.6$ (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.37$ (s, 1H), 8.70 (s, 1H), 7.34 (m, 5H), 5.50 (dd, 1H; *J* 10.14 Hz, *J* 8.76 Hz), 4.92 (dd, 1H; *J* 10.24 Hz, *J* 8.61 Hz), 4.41 (t, 1H; *J* 8.61 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 162.0$, 147.1, 146.4, 145.5, 144.2, 142.4, 141.2, 128.8, 127.9, 126.7, 75.3, 70.4 ppm. TOFMS ES$^+$ for $C_{13}H_{11}N_3O$ theoretical $[M+H]^+$: 226.0980; measured $[M+H]^+$: 226.0972. IR-TF (KBr pellets, cm^{-1}): 702.3; 1022.9; 1517.7; 1652.8; 2930.5; 3374.4.

4.2.2. (*S*)-4-Isopropyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole 2c

83%; Colorless oil; $[\alpha]_D = -38 \pm 2$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.26$ (s, 1H), 8.67 (s, 1H), 4.53 (m, 1H), 4.21 (m, 2H), 1.90 (m, 1H), 1.07 (d, 3H; *J* 3.75 Hz), 0.96 (d, 3H; *J* 3.75 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 160.7$, 146.1, 145.2, 144.1, 142.6, 73.1, 70.9, 32.7, 18.9, 18.1 ppm. TOFMS ES$^+$ for $C_{10}H_{13}N_3O$ theoretical $[M+H]^+$: 192.1137; measured $[M+H]^+$: 192.1128. IR-TF (KBr pellets, cm^{-1}): 668.4; 1020.6; 1533.8; 1675.5; 2963.4; 3390.4.

4.2.3. (*S*)-4-Benzyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole 2a

95%; Colorless oil; $[\alpha]_D = -18.5 \pm 2.2$ (*c* 1.035, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.27$ (s, 1H), 8.68 (s, 1H), 7.28 (m, $5H_{aromat}$), 4.71 (m, 1H), 4.48 (td, 1H; *J* 9.2 Hz), 4.26 (td, 1H; *J* 5.2 Hz), 3.30 (ddd, 1H; *J* 13.6 Hz, *J* 5.2 Hz), 2.81 (ddd, 1H; *J* 13.6 Hz, *J* 8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 161.3$, 146.3, 145.2, 144.1, 142.5, 137.4, 129.2, 128.6, 126.7, 72.5, 68.2, 41.4 ppm. TOFMS ES$^+$ for $C_{14}H_{13}N_3O$ theoretical $[M+H]^+$: 240.1137; measured $[M+H]^+$: 240.1137. IR-TF (KBr pellets, cm^{-1}): 699.5; 1021.5; 1533.7; 1652.8; 2921.1; 3362.9.

4.2.4. (*S*)-4-Methyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole 2d

91%; Yellow oil; $[\alpha]_D = -41.9 \pm 2.4$ (*c* 1.135, $CHCl_3$).^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.24$ (s, 1H), 8.66 (s, 2H), 4.58 (m, 1H), 4.48 (dd, 1H; *J* 15.87 Hz, *J* 8.01 Hz), 4.06 (m, 1H), 1.40 (dd, 3H; *J* 6.48 Hz, *J* 1.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 160.8$, 146.2, 145.1, 144.1, 142.5, 74.0, 62.5, 21.1 ppm. TOFMS ES$^+$ for $C_8H_{10}N_3O$ theoretical $[M+H]^+$: 164.0824; measured $[M+H]^+$: 164.0821. IR-TF (KBr pellets, cm^{-1}): 668.3; 1020.7; 1531.8; 1652.8; 2975.8; 3392.9.

4.2.5. (*S*)-5-Methyl-2-(pyrazin-2-yl)-4,5-dihydrooxazole 2e

82%; Yellow oil; $[\alpha]_D$ = +23 ± 4 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.41 (s, 1H), 8.77 (d, 1H; *J* 2.16 Hz), 8.55 (d, 1H; *J* 1.11 Hz), 4.08 (m, 1H), 3.69 (m, 1H), 3.38 (m, 1H), 1.29 (dd, 3H; *J* 6.36 Hz, *J* 0.99 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.8, 147.3, 145.1, 144.4, 142.5, 67.3, 46.8, 21.0 ppm. TOFMS ES$^+$ for $C_8H_{10}N_3O$ theoretical $[M+H]^+$: 164.0824; measured $[M+H]^+$: 164.0821. IR-TF (KBr pellets, cm^{-1}): 668.4; 1024.7; 1533.8; 1653.1; 2975.8; 3392.9.

4.2.6. (*S*)-4-Phenyl-2-(pyridin-2-yl)-4,5-dihydrooxazole 2f

82%; Yellow oil; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.75 (d, 1H; *J* 4.6 Hz), 8.18 (d, 1H; *J* 7.8 Hz), 7.78–7.85 (m, 1H), 7.29–7.47 (m, 5H), 5.42–5.52 (m, 1H), 4.87–4.96 (m, 1H), 4.40 (t, 1H; *J* 8.4 Hz) ppm. Data in agreement with the literature.[17]

4.2.7. (*S*)-4-Isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole 2g

73%; Colorless oil; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.27 (d, 1H; *J* 8.4 Hz), 8.23 (s, 2H), 7.84 (d, 2H; *J* 8.1 Hz), 7.77–7.72 (m, 1H), 7.59 (t, 1H; *J* 7.5 Hz), 4.64–4.56 (m, 1H), 4.36–4.17 (m, 2H), 2.03–1.90 (m, 1H), 1.08 (d, 3H; *J* 6.8 Hz), 0.97 (d, 3H; *J* 6.8 Hz) ppm. Data in agreement with the literature.[31]

4.2.8. (*S*)-2-(5-Chlorothiophen-2-yl)-4-phenyl-4,5-dihydrooxazole 2h

98%; Yellow oil; $[\alpha]_D$ = +6.4 ± 3.1 (*c* 0.44, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.54 (d, 1H; *J* 3.93 Hz), 7.32 (m, 5H), 6.95 (d, 1H; *J* 4.02 Hz), 5.38 (dd, 1H; *J* 8.16 Hz, *J* 9.87 Hz), 4.81 (dd, 1H; *J* 8.46 Hz, *J* 9.99 Hz), 4.30 (t, 1H; *J* 8.23 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.5, 141.7, 135.2, 130.3, 128.8, 128.3, 127.8, 127.0, 126.7, 75.3, 70.0 ppm. TOFMS ES$^+$ for $C_{13}H_{11}NOSCl$ theoretical $[M+H]^+$: 264.0250; measured $[M+H]^+$: 264.0250. IR-TF (KBr pellets, cm^{-1}): 698.9; 1034.0; 1250.3; 1437.4; 1533.9; 1646.1; 2921.4; 3028.7.

4.2.9. (*S*)-2-(5-Chlorothiophen-2-yl)-4-isopropyl-4,5-dihydrooxazole 2i

95%; Yellow oil; $[\alpha]_D$ = −36.9 ± 4 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.57 (d, 1H; *J* 2.72 Hz), 6.92 (d, 1H; *J* 3.98 Hz), 4.45 (m, 1H), 4.16 (m, 2H), 1.89 (m, 1H), 1.02 (d, 3H; *J* 6.58 Hz), 0.93 (d, 3H; *J* 10.02 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.7, 133.6, 130.7, 127.1, 71.8, 70.9, 32.5, 18.7, 17.9 ppm. TOFMS ES$^+$ for $C_{10}H_{13}NOSCl$ theoretical $[M+H]^+$: 230.0406; measured $[M+H]^+$: 230.0405. IR-TF (KBr pellets, cm^{-1}): 668.3; 803.1; 1042.2; 1276.4; 1436.7; 1538.3; 1646.0; 2875.3; 2965.9.

4.2.10. (*S*)-2-Cyclopropyl-4-phenyl-4,5-dihydrooxazole 2j

67%; Yellow oil; $[\alpha]_D$ = +25.3 ± 3.5 (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.30 (m, 5H), 5.15 (dd, 1H; *J* 7.86 Hz, *J* 10 Hz), 4.58 (dd, 1H; *J* 8.34 Hz, *J* 10 Hz), 4.06 (t, 1H; *J* 8.1 Hz), 1.77 (m, 1H), 0.99 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.0, 142.6, 128.6, 127.4, 126.5, 74.9, 69.3, 8.5, 7.3, 7.0 ppm. TOFMS ES$^+$ for $C_{12}H_{14}NO$ theoretical $[M+H]^+$: 188.1075; measured $[M+H]^+$: 188.1072. IR-TF (KBr pellets, cm^{-1}): 701.3; 1030.4; 1172.1; 1250.1; 1405.3; 1455.3;1540.3; 1646.1.

4.2.11. 1-((*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-methoxyethanol 2k

75%; Yellow oil; $[\alpha]_D$ = −51.5 ± 2.4 (*c* 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.83 (br s, 1H), 4.18 (m, 1H), 4.01 (m, 2H), 2.06 (s, 3H), 2.00 (s, 3H), 1.80 (m, 1H), 0.95 (d, 3H; *J* 4.38 Hz), 0.92 (d, 3H; *J* 2.42 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.1, 170.1, 64.4, 53.4, 29.4, 20.8, 19.2, 18.5 ppm. TOFMS ES$^+$ for $C_9H_{18}NO_3$ theoretical $[M+H]^+$: 188.1287; measured $[M+H]^+$: 188.1281. IR-TF (KBr pellets, cm^{-1}): 607.0; 1037.4; 1236.0; 1539.2; 1646.1; 2967.4; 3081.9.

4.2.12. (*S*)-2-(4-Chlorophenyl)-4-isopropyl-4,5-dihydrooxazole 2l

100%; Yellow oil; ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.90 (d, 2H; *J* 8.6 Hz), 7.38 (d, 2H; *J* 8.6 Hz), 4.37–4.47 (m, 1H), 4.04–4.20 (m, 2H), 1.82–1.92 (m, 1H), 1.03 (d, 3H; *J* 6.8 Hz), 0.93 (d, 3H; *J* 6.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 162.5, 137.3, 129.6, 128.5, 126.4, 72.6, 70.3, 32.8, 18.9, 18.0 ppm. Data in agreement with the literature.[33]

4.2.13. (*S*)-4-Benzyl-2-(naphthalen-1-yl)-4,5-dihydrooxazole 2m

76%; Colorless oil; $[\alpha]_D$ = +14 ± 1.9 (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 9.06 (dd, 1H; *J* 8.32 Hz, *J* 1.14 Hz), 8.10 (dd, 1H; *J* 7.24 Hz, *J* 1.28 Hz), 7.98 (d, 1H; *J* 8.64 Hz), 7.89 (dd, 1H; *J* 7.4 Hz, *J* 1.8 Hz), 7.54 (m, 3H), 7.31 (m, 5H), 4.78 (m, 1H), 4.44 (t, 1H, *J* 8.6 Hz), 4.24 (dd, 1H; *J* 8.48 Hz, *J* 7.28 Hz), 3.35 (dd, 1H; *J* 13.72 Hz, *J* 5.08 Hz), 2.90 (dd, 1H; *J* 13.72 Hz, *J* 8.48 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.9, 138.0, 133.7, 131.9, 131.1, 130.7, 129.3, 128.9, 128.5, 128.4, 127.2, 126.5, 126.4, 126.0, 124.6, 70.8, 68.6, 41.9 ppm. TOFMS ES$^+$ for $C_{20}H_{18}NO$ theoretical $[M+H]^+$: 288.1388; measured $[M+H]^+$: 288.1390. IR-TF (KBr pellets, cm^{-1}): 702.3; 777.4; 996.9; 1125.4; 1191.8; 1510.9; 1642.5; 2923.4; 3060.0.

4.2.14. (*S*)-4-Isopropyl-2-(naphthalen-1-yl)-4,5-dihydrooxazole 2n

70%; Yellow oil; $[\alpha]_D$ = −63.6 ± 1.9 (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.13 (d, 1H; *J* 8.55 Hz), 8.10 (d, 1H; *J* 7.23 Hz), 7.97 (d, 1H; *J* 5.19 Hz), 7.89 (d, 1H; *J* 8.13 Hz), 7.56 (m, 3H), 4.48 (dd, 1H; *J* 7.92 Hz, *J* 9 Hz), 4.25 (m, 2H), 1.98 (m, 1H), 1.14 (d, 3H ; *J* 6.75 Hz), 1.04 (d, 3H ; *J* 9.75 Hz) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.3, 133.7, 131.7, 131.2, 128.9, 128.4, 127.2, 126.4, 126.0, 124.7, 124.6, 73.3, 69.3, 32.9, 19.0, 18.3 ppm. TOFMS ES$^+$ for $C_{14}H_{13}N_3O$ theoretical $[M+H]^+$: 240.1388; measured $[M+H]^+$: 240.1392. IR-TF (KBr pellets, cm^{-1}): 777.7; 1025.3; 1123.1; 1359.2; 1465.2; 1590.5; 1652.6; 2958.5; 3050.2.

4.2.15. (*S*)-2-(4-Fluorophenyl)-4-isopropyl-4,5-dihydrooxazole 2o

93%; Yellow oil; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.92–7.98 (m, 2H), 7.04–7.27 (m, 2H), 4.35–4.42 (m, 1H), 4.04–4.15 (m, 2H), 1.81–1.87 (m, 1H), 1.02 (d, 3H; *J* 6.9 Hz), 0.91 (d, 3H; *J* 6.6 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.2, 162.9, 162.4, 130.5, 124.1, 115.4, 115.1, 72.6, 70.2, 32.8, 18.8, 18.0 ppm. Data in agreement with the literature.[33]

4.3. General one-pot procedure for the synthesis of 4-substituted-bis-oxazolines

The synthesis of 1,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)benzene **3** is representative. A G4 vial in a Monowave 300 vessel was charged with phthalonitrile (37.2 mg, 0.290 mmol, 1 equiv) mixed with L-valinol (65.8 mg, 0.638 mmol, 2.2 equiv). The resulting mixture was irradiated using the closed vessel mode at 150 °C for 60 min. The reaction mixture was quenched with ethyl acetate and filtered through silica. The filtrate was dried over magnesium sulfate, and concentrated by rota-evaporation under vacuum to give the corresponding 1,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)benzene **1a** (87 mg, 0.289 mmol, 100% yield) as a colorless oil.

4.3.1. 1,2-Bis((*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)benzene 1a

100%; Yellow oil; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.76 (dd, 1H; *J* 6 Hz, *J* 3.6 Hz), 7.47 (dd, 1H; *J* 6 Hz, *J* 3.3 Hz), 4.34–4.43 (m, 1H), 4.05–4.14 (m, 2H), 1.86–1.92 (m, 1H), 1.05 (d, 3H; *J* 6.9 Hz), 0.96 (d, 3H; *J* 6.6 Hz) ppm. Data in agreement with literature.[16]

Acknowledgments

The authors are grateful to the DGRS (Direction Generale de la Recherche Scientifique) of the Tunisian Ministry of Higher Education, Scientific Research and Information and Communication Technologies, the CNRS, the University of Versailles Saint Quentin-en-Yvelines, France, and ANR (ANR-11-BS07-030-01), France, for the financial support.

References

1. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
2. Meyers, A. I.; Temple, D. L.; Haidukewych, D. E.; Mihelich, D. *J. Org. Chem.* **1974**, *39*, 2787.
3. Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375.
4. Hoarau, O.; Haddou-Ait, H.; Castro, M.; Balavoine, G. G. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3755.
5. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726; (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.
6. (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561; (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2011**, *111*, PR284.
7. Takahashi, S.; Togo, H. *Synthesis* **2009**, 2329.
8. (a) Nishiyama, H.; Ito, J.-H.; Shiomi, T.; Hashimoto, T.; Miyakawa, T.; Kitase, M. *Pure Appl. Chem.* **2008**, *60*, 743; (b) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353; (c) Schwekendiek, K.; Glorius, F. *Synthesis* **2006**, 2996.
9. Sharma, R.; Vadivel, S. K.; Duclos, R. I., Jr.; Makriyannis, A. *Tetrahedron Lett.* **2009**, *50*, 5780–5782.
10. Carmona, R. C.; Schevciw, E. P.; Albuquerque, J. L. P.; Wendler, E. P.; Dos Santos, A. A. *Green Proc. Synth.* **2013**, *2*, 35–42.
11. Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
12. Garcia, J. I.; Mayoral, J. A.; Pires, E.; Villalba, I. *Tetrahedron: Asymmetry* **2006**, *17*, 2270.
13. (a) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **2006**, *124*, 1173; (b) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Synlett* **2005**, 2321.
14. (a) Pieters, G.; Gaucher, A.; Prim, D.; Marrot, J. *Chem. Commun.* **2009**, 4827; (b) Pieters, G.; Gaucher, A.; Prim, D.; Besson, T.; Giner Planas, J.; Teixidor, F.; Viñas, C.; Light, M. E.; Hursthouse, M. B. *Chem. Commun.* **2011**, 772; (c) Pieters, G.; Gaucher, A.; Marque, S.; Maurel, F.; Lesot, P.; Prim, D. *J. Org. Chem.* **2010**, *75*, 2096; (d) Hassine, B. B. et al *Bull. Soc. Chem. Belg.* **1986**, *95*, 547; (e) Hassani, R.; Kacem, Y.; Mansour, H. B.; Ammar, H. B.; Hassine, B. B. *Chem. Biol. Interact.* **2014**, *217*, 41–48.
15. Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 996.
16. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.
17. (a) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1; (b) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499; (c) Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821; (d) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846; (e) Balavoine, G.; Clinet, J.; Lellouche, L. *Tetrahedron Lett.* **1989**, *30*, 5141.
18. (a) Johnson, J. S.; Evans, D. E. *Acc. Chem. Res.* **2000**, *33*, 325; (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thornauge, J. *Acc. Chem. Res.* **1999**, *32*, 605; (c) Ghosh, A.-K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1; (d) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189; (e) Reiser, O. *Nachr. Chem. Tech. Lab.* **1996**, *44*, 744.
19. Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 813.
20. Hall, J.; Lehn, J. M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.
21. Gerisch, M.; Krumper, J. P.; Bergman, R. G.; Tilley, T. D. *Organometallics* **2003**, *22*, 47.
22. Bazgir, A.; Amini, M. M.; Fazaeli, Y. *Open Catal. J.* **2009**, *2*, 163.
23. Jnaneshwara, G. K.; Deshpande, V. H.; Lalithambika, M.; Ravindranathan, H. T.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 459–462.
24. Baltork, I. M.; Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Zolfigol, M. A.; Alibeik, M. A.; Khosropour, A. R.; Kargar, H.; Hojati, S. F. *Catal. Commun.* **2008**, *9*, 894–901.
25. Baltork, I. M.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Hojati, S. F. *Catal. Commun.* **2008**, *9*, 1153–1161.
26. Shaabani, A.; Seyyedhamzeh, M.; Maleki, A.; Rezazadeh, F. *Appl. Catal. A: General* **2009**, *358*, 146.
27. Hojati, S. F.; Nezhadhoseiny, S. A. *J. Serb. Chem. Soc.* **2012**, *9*, 1181–1189.
28. Prasad, A. S.; Satyanarayana, B. *Der Pharm. Chem.* **2012**, *4*, 93.
29. Haixia, G.; Ping, L.; Xiangnan, L.; Wei, S.; Jianli, L.; Bingqin, Y.; Zhen, S. *Tetrahedron* **2013**, *69*, 6591–6597.
30. (a) Touati, R.; Hassine, B. B.; Genet, G. P. *C.R. Acad. Sci.* **2000**, *3*, 35–42; (b) Bahy, A.; Jegham, N.; Kacem, Y.; Marrot, J.; Hassine, B. B. *J. Soc. Chim. Tunis.* **2012**, *14*, 137–145.
31. Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543–550.
32. C. Bunt et al.[33] have synthesized these two products in a multi-step sequence according to literature protocols starting from the corresponding 4-substituted acids or acid chlorides and (*S*)-valinol.[34]
33. Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, *5*, 2279.
34. Peer, M.; Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprintz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547.
35. Comparison of yields obtained herein with literature data. **3**, present work 100%; lit.[36] 92%; lit.[16] 89%.
36. Gomez, M.; Jansat, S.; Muller, G.; Maestro, M. A.; Saavedra, J. M.; Font-Bardia, M.; Solans, X. *J. Chem. Soc., Dalton Trans* **2001**, 1432–1439.
37. **2k** was obtained as a mixture of diastereomers.