Solvent-Free Microwave-Assisted Efficient Synthesis of 4,4-Disubstituted 2-Oxazolines

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4,4-Disubstituted 2-oxazolines have been synthesized by a microwave-promoted solvent-free direct condensation of carboxylic acids and disubstituted β-amino alcohols in good to excellent yields. Zinc oxide is a very good solid support in cases where a Lewis acid is required. The method described herein is a very good, safe, clean, economical, and environmentally friendly alternative to the classical procedures.

Introduction

2-Oxazolines constitute a wide family of five-membered heterocycles with important applications in the fields of organic synthesis[1] and pharmacology.[2,3] These heterocycles are readily prepared from *N*-acyl derivatives of β-hydroxylamines by heating or by the action of a dehydrating agent such as thionyl chloride, sulfuric acid, or phosphorous pentoxide.[4] The direct condensation of carboxylic acids with β-hydroxylamines requires high temperatures and strongly acidic conditions,[3] and is therefore not a synthetically valuable method to access these heterocycles. Alternative procedures using imino ether hydrochlorides, nitriles and isocyanides have been described.[4] Vorbrüggen et al.[3] have developed a one-pot protocol for the transformation of carboxylic acids into 2-oxazolines using Ph_3P/CCl_4 as a chemical activator. Natale et al.[5] have shown that carboxylate esters can be directly transformed into 2-oxazolines using lanthanide chloride as catalyst.

Organic synthesis assisted by microwave (MW) has seen spectacular growth over the last few years.[6,7] Particularly when this new technique has been coupled with solvent-free procedures, resulting in clean, easy-to-perform, cheap, safe and environmentally friendly conditions which are widely used as synthetic tools[8−10] under "Green Chemistry" conditions.[11] Furthermore, the development of monomode reactors, taking advantage of wave focussing and accurate control of temperature by infrared detection[12] (and its monitoring according to emitted MW power), has enhanced this technique mainly due to better reproducibility and predictability of results and, in turns better control and optimization of the procedures.

We have shown in a preliminary communication[13] that some 4,4-bis(hydroxymethyl)-2-oxazolines are easily obtained from the direct, solvent-free microwave-assisted condensation of carboxylic acids **1** with the β-amino alcohol **2a** (Table 1). In this paper we report the extension of this procedure to the synthesis of a wide set of 4,4-disubstituted 2-oxazolines **3a−i** (Table 1). While the microwave-assisted solvent-free direct condensation of the carboxylic acids **1a−i** with the β-amino alcohols **2a** and **2b** afforded 2-oxazolines **3(a−f)(a−b)** in very good yields (Table 2), the reactions with **2c** called for a Lewis acidic solid support (Table 3).

Results and Discussion

Perreux and Loupy[14] have rationalized the still controversial specific microwave effect[14,15] in organic synthesis on the basis of medium effects and mechanistic considerations. They postulate that a bimolecular reaction between neutral reactants should be assisted by microwave irradiation as the reaction goes through a dipolar transition state (TS). This dipolar transition state (TS) is prone to develop more ef-

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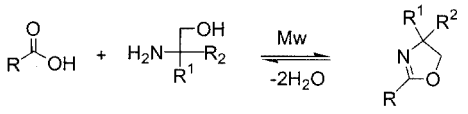
Table 1. 2-Oxazolines synthesized in this work



1a–i **2a–c** **3(a–i)a** **3(b–i)b** **3(c–i)c**

Carboxylic acid	Amino alcohol	2-Oxazoline	R	R^1	R^2
1a	**2a**	**3aa**	C_6H_5	CH_2OH	CH_2OH
1a	**2b**	**3ab**	C_6H_5	$CH_2OCOC_6H_5$	CH_3
1a	**2c**	**3ac**	C_6H_5	CH_3	CH_3
1b	**2a**	**3ba**	C_4H_3O	CH_2OH	CH_2OH
1b	**2c**	**3bc**	C_4H_3O	CH_3	CH_3
1c	**2a**	**3ca**	$C_{17}H_{35}$	CH_2OH	CH_2OH
1c	**2a**	**3cabis**	$C_{17}H_{35}$	$CH_2OCOC_{17}H_{35}$	$CH_2OCOC_{17}H_{35}$
1c	**2b**	**3cb**	$C_{17}H_{35}$	CH_3	$CH_2OCOC_{17}H_{35}$
1d	**2a**	**3da**	*o*-Cl-C_6H_4	CH_2OH	CH_2OH
1e	**2a**	**3ea**	*m*-Cl-C_6H_4	CH_2OH	CH_2OH
1f	**2a**	**3fa**	*p*-Cl-C_6H_4	CH_2OH	CH_2OH
1g	**2c**	**3gc**	*p*-OCH_3–C_6H_4	CH_3	CH_3
1h	**2c**	**3hc**	*p*-NO_2–C_6H_4	CH_3	CH_3
1i	**2c**	**3ic**	$C_{15}H_{31}$	CH_3	CH_3

ficient stabilizing electrostatic interactions with the applied electromagnetic field (of a dipole-dipole nature) than the neutral ground state (GS) due to dipole apparition during the course of the reaction. This results in a decrease in the energy of activation. As a corollary, as the TS is displaced further along the reaction coordinates (more product-like TS) the more prone it will be to develop an increased polarity and the more pronounced will be the microwave effect.

The condensation reaction between amines and carboxylic acids leading to amides fulfils the above requirements. As expected, the microwave-assisted solvent-free direct preparation of amides from carboxylic acids and amines has been described to proceed smoothly and in good yields.[16–20] In the case of β-amino alcohols, once the amides are formed, subsequent intramolecular condensation between the amides and the free hydroxyl groups present in the molecule can afford 2-oxazolines (Table 1).

Because of the polar nature of the transition states involved in these processes, the microwave irradiation should help to drive the reaction to completion. Furthermore, the final temperature reached ($T > 150$ °C) implies that the formed water is removed from the reaction medium rendering the global process irreversible, irrespective of the mode of activation (MW irradiation or conventional heating). With this idea in mind, we have irradiated several solid mixtures of carboxylic acids **1a–i** and β-amino alcohols **2a–c**

Table 2. Solvent-free microwave-assisted synthesis of 2-oxazolines **3(a-f)(a-b)** by reacting equivalent amounts (10 mmol) of **1** and **2**

Entry	Microwave equipment	Power (W)	Time (min)	Final temp. (°C)	Product	Yield (%)
1	Multimode	850	3.25	206	**3aa**	88
	Monomode	90	6	223	**3aa**	84
2	Multimode	850	3	200	**3ba**	81
	Monomode	90	4	197	**3ba**	84
3	Multimode	850	10	220	**3ca**	95
	Multimode	850	6	204	**3cabis**[a]	97
	Monomode	300	13	214	**3ca**	97
4	Multimode	850	3.5	210	**3da**	52
	Monomode	150	5	200	**3da**	80
5	Multimode	850	3.4	228	**3ea**	55
	Monomode	150	3	202	**3ea**	80
6	Multimode	850	5.5	230	**3fa**	60
	Monomode	300	5	200	**3fa**	95
7	Multimode	850	13	210	**3cb**[b]	97
8	Multimode	850	3.5	198	**3ab**[b]	94
	Monomode	150	5	219	**3ab**[b]	96

[a] 3 equiv. of carboxylic acid was used. [b] 2 equiv. of carboxylic acid was used.

to obtain the five-membered heterocycles according to a one-step procedure.

Tables 2 and 3 summarizes the yields obtained and experimental conditions under MW irradiation using two kinds of equipment, either a domestic oven (multimode) or a monomode reactor with focused waves (Prolabo S402 and Maxidigest MX350 systems).

From Table 2 it is obvious, as found in a lot of cases[21−26] that the monomode reactor leads to better yields than the multimode oven and requires a lower irradiation power level (entries 4, 5, and 6). The electronic nature of the R group does not seem to be a limiting factor and both aliphatic and aromatic carboxylic acids can be used with the same efficiency (entries 1, 2, 3, and 8). When more than one equivalent of the carboxylic acid is used, further esterification of the free hydroxyl groups on the heterocycles takes place to give the mono- or di-ester derivatives (entries 3, 7, and 8). The presence of at least two hydroxyl groups in the amino alcohol seems to be crucial to promote the further condensation. In the absence of such a second hydroxyl group, the condensation needs a catalyst to proceed and we found that zinc oxide was a very convenient additive. We believe that the key role of the second hydroxyl group is to form an internal H-bond with the carbonyl group of the amide to provide some electrophilic assistance for the next condensation. This mechanism is also highly propitious for MW specific effects as it involves a dipolar TS from neutral reactants (Figure 1).

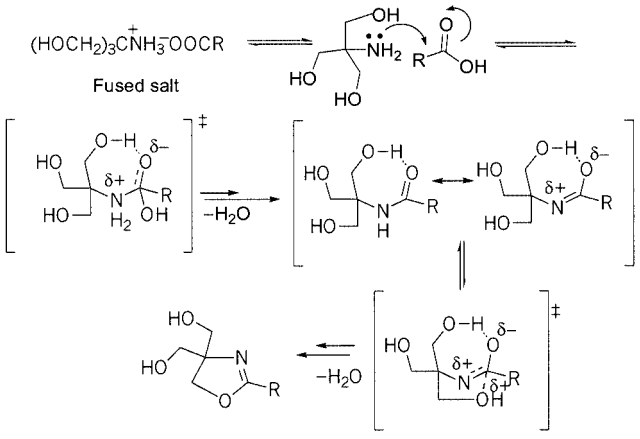


Figure 1. Mechanism of the synthesis of 2-oxazolines from a carboxylic acid and a β-amino alcohol

While the irradiation of the mixtures containing **2a** or **2b** afforded 2-oxazolines in excellent yields irrespective of the carboxylic acid used (Table 2), those involving **2c** failed to give the expected heterocycles.[27] In these cases, the process requires a solid acid support to go to completion. For this purpose, zinc oxide was found to be the most efficient. It acts both as a solid support and as a soft Lewis acid catalyst. Other acidic solid supports (montmorillonites KSF and K10, calcinated Al_2O_3, SiO_2) were unsuccessful (Table 3).

The zinc oxide seems to play a double role: it creates a polar environment for the microwave catalysis[28] (polar solid support) and activates the carbonyl group for the condensation (Lewis acid catalyst). The results summarized in Table 3 show that the monomode is here again more effective than the multimode (entry 1) and that the method is quite general and insensitive to the electronic nature of the carboxylic acid used (entries 3, 4, and 5).

The existence of specific microwave effects[6] was evident since the same reactions using a thermostatted oil-bath under identical conditions as for the microwave-assisted reactions gave only traces of the heterocycles.

Conclusion

In summary, we have shown that the synthesis of 4,4-disubstituted 2-oxazolines by direct condensation of a carboxylic acid and a substituted β-amino alcohol is feasible using microwave technology under solvent-free conditions. Zinc oxide can be used as a solid support in those cases in which a Lewis acid is required. The process is safe, clean, economical, and environmentally friendly.

Experimental Section

General Remarks: Melting points are uncorrected and were determined in a Reichter Thermovar apparatus. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ or [D_6]DMSO solutions were recorded either at 250 MHz or 200 and 50 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2−500), respectively. FT-IR spectra were registered as KBr discs or chloroform solutions using a Shimadzu IR-408 spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett−Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were per-

Table 3. Synthesis of 4,4-dimethyl 2-oxazolines **3(a-i)c** by reacting **1** and **2c** impregnated on zinc oxide under MW solvent-free conditions

Entry	Microwave equipment	Power (W)	Time (min)	Final temp. (°C)	Product	Yield (%)
1	Multimode	850	0.25	205	**3ac**	78
	Monomode	60	3	185	**3ac**	90
2	Monomode	150	0.5	203	**3bc**	83
3	Monomode	60	9	208	**3gc**	91
4	Monomode	60	4	220	**3hc**	76
5	Monomode	60	5	220	**3ic**	84

formed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyser. Analytical thin-layer chromatography plates used were E. Merck Brinkman Uvactive silica gel (Kieselgel 60 F254) on aluminium. Reactions were performed in a domestic microwave oven Goldstar Model MA 1197M (850 watt), a Maxidigest MX350 modified monomode reactor or a S402 from Prolabo. Compound names were obtained using the ACD/I-Lab Web service (ACD/IUPAC Name Free 6.00). Oxazolines **3aa**, **3ba**, and **3ca** have been fully described in our preliminary communication.[13] Oxazoline **3ac** is commercial.

2-Oxazolines 3(a−f)(a−b). General Procedure: Finely powdered carboxylic acid (10 mmoles) and β-amino alcohol (10 mmoles) were placed in a Pyrex flask in such a way as to occupy only 10% of the overall volume. The mixture was irradiated using the mode and power indicated in Table 2 and monitored by TLC. When the irradiation was performed in a domestic oven, the sample was placed in the hottest zone of the oven, previously determined after careful cartography of the oven.[29] When the irradiation was performed in the monomode reactor the reaction mixture was mechanically stirred for better homogenization. When all the starting material had disappeared, the irradiation was terminated and the mixture was allowed to cool to room temperature. Diethyl ether was added and the resulting mixture was filtered. The solid oxazoline was further washed with diethyl ether and recrystallized from the appropriate solvent.

[2-(2-Chlorophenyl)-4,5-dihydro-1,3-oxazole-4,4-diyl]dimethanol (3da): Mol. mass 241.68; 80% yield (1.93 g); m.p. 136−137 °C (isopropyl alcohol) (ref.[30] 138−139 °C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3428 (OH), 1653 (C=N). ^1H NMR (250 MHz, [D$_6$]DMSO, ppm): δ = 3.47 (br. s, 4 H, 2 × CH_2OH), 4.32 (s, 2 H, 2 × 5-H), 7.48−7.86 (m, 4 H, Ar-H). ^{13}C NMR (50 MHz, [D$_6$]DMSO, ppm): δ = 63.9, 70.8, 78.2, 127.3, 127.7, 129.3, 130.1, 130.3, 132.4, 161.2 (2 × C). $C_{11}H_{12}ClNO_3$: calcd. C 54.67, H 5.00, N 5.80, Cl 14.67; found C 54.37, H4.85, N 5.81, Cl 14.74.

[2-(3-Chlorophenyl)-4,5-dihydro-1,3-oxazole-4,4-diyl]dimethanol (3ea): Mol. mass 241.68; 80% yield (1.93 g); m.p. 114−115 °C (isopropyl alcohol) (ref.[30] 113−115 °C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3428 (OH), 1633 (C=N). ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 2.5−3.5 (m, 2 H, 2 × OH), 3.73 (d, J = 12 Hz, 4 H, 2 × CH_2OH), 4.38 (s, 2 H, 2 × 5-H), 7.2−7.8 (m, 4 H, Ar-H). ^{13}C NMR (50 MHz, [D$_6$]DMSO, ppm): δ = 63.9, 70.8, 77.2, 127.3, 127.7, 129.3, 130.1, 130.3, 132.4, 161.2 (2 × C).

[2-(4-Chlorophenyl)-4,5-dihydro-1,3-oxazole-4,4-diyl]dimethanol (3fa): Mol. mass 241.68; 95% yield (2.3 g); mp. 178−179 °C (isopropyl alcohol) (ref.[31] 177−178 °C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3428 (OH), 1642 (C=N). ^1H NMR (250 MHz, [D$_6$]DMSO, ppm): δ = 3.76 (d, J = 11 Hz, 4 H, 2 × CH_2OH), 4.40 (s, 2 H, 2 × 5-H), 7.4 (d, J = 11 Hz, 2 H, 2 × Ar-H), 7.84 (d, J = 11 Hz, 2 H, 2 × Ar-H). ^{13}C NMR (50 MHz, [D$_6$]DMSO, ppm): δ = 63.9, 70.8, 77.1, 126.5 (2 × C), 127.7 (2 × C), 130.4, 135.9, 161.3 (2 × C).

(2-Heptadecyl-4,5-dihydro-1,3-oxazole-4,4-diyl)di(methylene) Dioctadecanoate (3cabis): Mol. mass 902.54; 97% yield (8.75 g); m.p. 83−84 °C ($CHCl_3$/MeOH, 1:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1740 (C=O), 1668 (C=N). ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 0.9 (t, 9 H, J = 7 Hz, 3 × Me), 1.26 (m, 84 H, 42 × CH_2), 1.60 (m, 6 H, 3 × CH_2), 2.3 (t, J = 8 Hz, 2 H, CH_2CN), 2.32 (t, J = 8 Hz, 2 H, CH_2CO), 4.08 (s, 2 H, 2 × 5-H), 4.14 (d, J = 11 Hz, 4 H, CH_2OCO). $C_{57}H_{109}NO_5$: calcd. C 77.19, H 12.40, N 1.55; found C 77.66, H 12.49, N 1.47.

(4-Methyl-4,5-dihydro-2-phenyl-1,3-oxazol-4-yl)methyl Benzoate (3ab): Mol. mass 295.34; 96% yield (2.84 g); m.p. 45−47 °C (isopropyl alcohol). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1727 (C=O), 1649 (C=N). ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 1.5 (s, 3 H, Me), 4.38 (s, 2 H, 2 × 5-H), 4.5 (d, J = 9 Hz, 2 H, CH_2OCO), 7.4 (m, 6 H, Ar-H), 8.0 (m, 4 H, Ar-H). HRMS (CI) (NH_3): m/z= 296 [M + 1].

(2-Heptadecyl-4-methyl-4,5-dihydro-1,3-oxazol-4-yl)methyl Octadecanoate (3cb): Mol. mass 620.06; 97% yield (6.01 g); m.p. 67−68 °C ($CHCl_3$/MeOH, 1:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1732 (C=O), 1662 (C=N). ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 0.9 (t, J = 7 Hz, 6 H, 3 × Me), 1.26 (m, 56 H, 28 × CH_2), 1.30 (s, 3 H, Me), 1.63 (m, 4 H, 2 × CH_2), 2.27 (t, J = 8 Hz, 2 H, CH_2CN), 2.30 (t, J = 8 Hz, 2 H, CH_2COO), 3.99 (d, J = 9 Hz, 4 H, 2 × 5-H), 4.02 (d, J = 11 Hz, 2 H, CH_2OCO).$C_{40}H_{77}NO_3$: calcd. C 77.48, H 12.52, N 2.26; found C 77.50, H 12.45, N1.99.

2-Oxazolines 3(a−i)c. General Procedure: Zinc oxide (47.4 g, 580 mmol) was added to a round-bottomed flask containing a solution of the carboxylic acid (20 mmoles) in an aprotic solvent (50 mL of CH_2Cl_2, EtOAc or Et_2O depending on the case). A solution of the amino alcohol **2c** (30 mmol) in the same solvent (50 mL) was added to the vigorously stirred mixture. The mixture was further stirred at room temperature for a few minutes and then the solvent was evaporated until total dryness. The resulting solid was powdered and introduced into a Pyrex flask in such a way as to occupy only 10% of the overall volume. The mixture was then irradiated using the mode and power indicated in Table 3 and monitored by TLC. When the irradiation was performed in the monomode reactor the sample was mechanically stirred for better homogenization. When all the starting material had disappeared, the irradiation was terminated and the mixture was allowed to cool to room temperature. Ethyl acetate was added and the resulting mixture was centrifuged. The clear liquid was taken out and the process repeated at least twice. The liquid phases were collected and filtered through a pad of SiO_2/Al_2O_3 (1:1 w/w) to remove the last traces of zinc oxide. The filtrate was concentrated to give the pure oxazoline derivative.

2-(2-Furyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (3bc): Mol. mass 165.19; 83% yield (2.74 g). IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 1672 (C=N). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 1.35 (s, 6 H, 2 × Me), 4.06 (s, 2 H, 2 × 5-H), 6.45 (m, 1 H, Fur-H), 6.91 (d, J = 3.4 Hz, 1 H, Fur-H), 7.5 (d, J = 1 Hz, 1 H, Fur-H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 28.1, 67.4, 78.9, 111.2, 113.8, 142.9, 144.8, 154.5 (2 C). HRMS (EI): calcd. for $C_9H_{11}NO_2$: 165.078979; found 165.079720.

4,5-Dihydro-2-(4-methoxyphenyl)-4,4-dimethyl-1,3-oxazole (3gc): Mol. mass 205.26; 91% yield (3.74 g). IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 1645 (C=N). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 1.35 (s, 6 H, 2 × Me), 3.82 (s, 3 H, OMe), 4.06 (s, 2 H, 2 × 5-H), 6.88 (d, J = 9 Hz, 1 H, Ar-H), 7.86 (d, J = 9 Hz, 1 H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 28.1, 55.1, 67.3, 78.9 (2 C), 113.5, 115.7, 120.4 (2 C), 129.8, 161.8 (2 C). HRMS (EI): calcd. for $C_{12}H_{15}NO_2$: 205.110279; found 205.108467.

4,5-Dihydro-4,4-dimethyl-2-(4-nitrophenyl)-1,3-oxazole (3hc): Mol. mass 220.23; 76% yield (3.35 g); mp. 90−91.5 °C ($CHCl_3$, cm^{-1}). IR ($CHCl_3$): $\tilde{\nu}$ = 1649 (C=N), 1525 (NO_2), 1351 (NO_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 6 H, 2 × Me), 4.15 (s, 2 H, 2 × 5-H), 8.09 (d, J = 9 Hz, 1 H, Ar-H), 8.24 (d, J = 9 Hz, 1 H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 28.2, 68.1, 79.5 (2 C). 123.3 (2 C), 129.1, 133.8, 149.3, 160.2 (2 C). $C_{11}H_{12}N_2O_3$: calcd. C 59.99, H 5.49, N 12.72; found C 59.76, H 5.29, N 12.59.

4,5-Dihydro-4,4-dimethyl-2-pentadecyl-1,3-oxazole (3ic): Mol. mass 309.54; 84% yield (5.2 g). IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 1664 (C=N). ^1H

NMR (200 MHz, $CDCl_3$, ppm): δ = 0.84 (t, *J* = 7 Hz, 3 H, Me), 1.22 (br. s, 30 H, 12 × CH_2 and 2 × Me), 1.57 (m, 2 H, CH_2), 2.20 (t, *J* = 7 Hz, 2 H, CH_2CN) 3.85 (s, 2 H, 2 × 5-H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ = 22.2, 25.6, 27.6 (2 C), 27.9, 28.7, 28.8, 29, 29.1 (3 C), 29.3, 66.3, 78.3, 165.5 (6 C). HRMS (EI): calcd. for $C_{20}H_{39}NO$: 309.303165; found 309.300774.

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