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Open vessel mode microwave-assisted synthesis of 2-oxazolines from carboxylic acids

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ABSTRACT

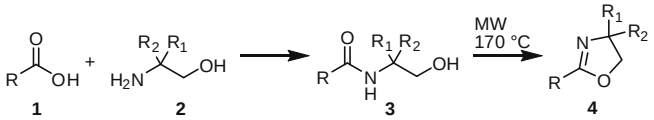
Microwave-assisted synthesis of 2-oxazolines from carboxylic acids using the open vessel technique is described. This efficient method involves direct condensation of carboxylic acids with excess 2-amino-2-methyl-1-propanol at 170 °C to give the corresponding 2-oxazolines in moderate to excellent yields.

1. Introduction

Oxazolines have been of great interest[1] due to their versatility as protecting groups,[2] as chiral auxiliaries in asymmetric synthesis,[3] and as ligands for asymmetric catalysis.[4] Various methods have been developed for the preparation of 2-oxazolines from carboxylic acids. One early method (see Scheme 1) used conventional heating of equimolar concentrations of carboxylic acids **1** and 2-aminoethanol (**2a**, $R_1 = R_2 = H$) at 200 °C followed by dehydration of *N*-acyl-2-aminoethanols **3a** using phosphorous pentoxide to generate oxazolines **4a**;[5] thionyl chloride and other reagents have also been used.[1] A recent method used 2-chloro-4,6-dimethoxy-1,3,5-triazine and *N*-methylmorpholine to generate a complex (1 equiv), which upon treatment with carboxylic acids **1** and 3 equiv of 2-amino-2-methyl-1-propanol (**2b**, $R_1 = R_2 = CH_3$) at room temperature, gave the corresponding oxazolines **4b**.[6] More recently, Kangani and Kelley[7] reported using bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor, 2.2 equiv) with carboxylic acids **1** in the one-pot synthesis of amides from secondary amines or 2-oxazolines **4b** from 1.8 equiv of 2-amino-2-methyl-1-propanol (**2b**) at 0 °C. This method reportedly worked better than the triazine complex[6] coupling for aliphatic and benzoic acids. We were unable to prepare the corresponding 2-oxazoline of 3,5-dimethoxyphenylacetic acid by this method, however. We now report a general and efficient method which is a variation of the direct synthesis[8–10] of 2-oxazolines from carboxylic acids.

2. Results and discussion

The use of microwave heating in organic chemistry has become a valuable tool in drug discovery to carry out reactions more efficiently than the use of conventional heating by offering improved reaction yields, decreased reaction times, and solvent-free conditions.[11,12] During the course of our work in the characterization of the endocannabinoid metabolome, we recently converted the carboxylic acid moieties of various fatty acids associated with endocannabinoids to 4,4-bis(hydroxymethyl)-2-oxazolines **4c** ($R_1 = R_2 = CH_2OH$) using tris(hydroxymethyl)aminomethane **2c** ($R_1 = R_2 = CH_2OH$) with microwave heating.[10] We have now extended this methodology by transforming various carboxylic acids into their corresponding 2-substituted 4,4-dimethyl-2-oxazolines **4b** ($R_1 = R_2 = CH_3$) with microwave heating using 2-amino-2-methyl-1-propanol **2b** (see Table 1). Various carboxylic acids and microwave heating conditions were studied for this transformation. Microwave heating in closed vessels led to



a $-R_1 = -R_2 = -H$
b $-R_1 = -R_2 = -CH_3$
c $-R_1 = -R_2 = -CH_2OH$

Scheme 1. Reaction of carboxylic acids **1** with 2-aminoalcohols **2** to give 2-oxazolines **4**.

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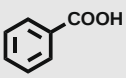
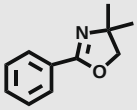
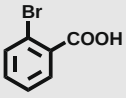
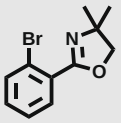
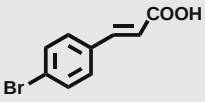
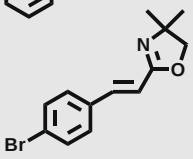
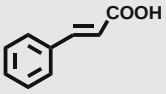
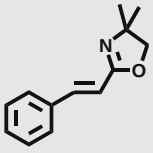
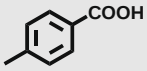
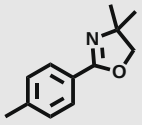
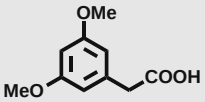
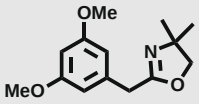
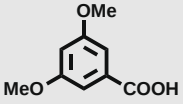
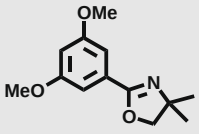
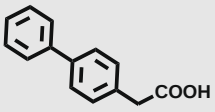
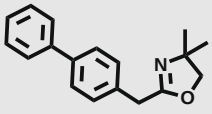
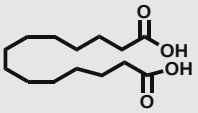
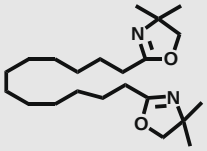
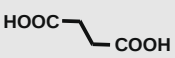
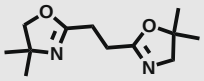
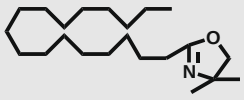
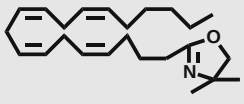
Table 1
Synthesis of 2-oxazolines **4b** from carboxylic acids **1** using open vessel mode microwave heating

Entry	Acid	Oxazoline product	Reaction conditions	% Yield
1			170 °C, 15 min	85
2			170 °C, 15 min	78
3			170 °C, 15 min	79
4			170 °C, 15 min	83
5			170 °C, 15 min	81
6			170 °C, 15 min	73
7			170 °C, 15 min	71
8			170 °C, 15 min	80
9			170 °C, 25 min	78
10			170 °C, 25 min	82
11			170 °C, 40 min	73
12			170 °C, 25 min	78

intermediate amide **3b** formation, but not to cyclization. However, by performing the reaction in an open vessel mode, which allows for the dehydration of the amide **3b** intermediates, the 2-oxazoline **4b** products were prepared in moderate to high yields.

Open vessel mode microwave heating of carboxylic acids in excess 2-amino-2-methyl-1-propanol **2b** without solvent at 150 °C for 5 min led to intermediate amides **3b** with very little oxazoline **4b** formation. The optimized reaction conditions required heating at 170 °C for 15 min, except for entries 9, 10, and 12 which required 25 min and entry 11 that required 40 min for oxazoline formation. Longer heating tends to result in more decomposition byproducts. Yields of 2-phenyl (entry 1, 85%; lit.[6] 78%; lit.[7] 97%; lit.[9] 90%) and aliphatic (entry 11, 73%; lit.[6] 82%; lit.[7] 99%; lit.[9] 84%) 2-oxazolines were comparable to those obtained through the mild methods using coupling and dehydrating reagents or zinc oxide-assisted microwave conditions for these thermally stable carboxylic acids. In addition to aliphatic and aromatic carboxylic acids, entries 3, 4, and 12 demonstrate the application of this open vessel methodology to unsaturated carboxylic acids. The method was also successfully applied to dicarboxylic acids as demonstrated by entries 9 and 10. We were unable to prepare the corresponding 2-oxazoline **4b** of 3,5-dimethoxyphenylacetic acid using Deoxo-Fluor, but obtained a 73% isolated yield (entry 6) using open vessel microwave heating with 6 equiv of 2-amino-2-methyl-1-propanol **2b** at 170 °C for 15 min. A comparable 68% isolated yield of this oxazoline **4b** was obtained from 3,5-dimethoxyphenylacetic acid using 2 equiv of 2-aminoalcohol **2b** with longer heating (40 min) conditions, and when using 1 equiv of 2-aminoalcohol **2b** , a 60% isolated yield was obtained after 40 min. Thus, using an excess of 2-aminoalcohol **2b**, when possible, results in higher conversion to 2-oxazoline, less amide intermediate and other byproduct impurity, and less product decomposition.

3. Conclusions

The reported method proved to be simple and efficient for the conversion of carboxylic acids into 2-oxazolines in good yields. Unlike some of the previously reported methods, our microwave open vessel technique requires only the reactants (solvent-free), relatively short reaction times, and simple chromatographic purifications.

4. Typical procedure

The 3,5-dimethoxyphenyl acetic acid (500 mg, 2.55 mmol) was mixed with 2-methyl-2-aminopropanol **2b** (1.36 g, 15.3 mmol, 6 equiv) in a CEM microwave vessel. The resulting mixture was irradiated using the open vessel mode at 170 °C for 15 min. The reaction mixture was quenched with water (4 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, and concentrated by rotoevaporation under vacuum to give the crude product, which was then chromatographed on silica gel using a Biotage SP2 eluting with acetone/hexane (0–30% acetone gradient) to give the corresponding 2-(3,5-dimethoxyphenylmethyl)-2-oxazoline **4b** (464 mg, 1.86 mmol, 73% yield, entry 6) as a faint yellow liquid product that was homogeneous by TLC (40:60 acetone/hexane, R_f 0.65).

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Supplementary data

Supplementary data (characterizations and ^{1}H NMR spectra of all 2-oxazoline **4b** products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.079.

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