Communication

Synthesis of methyl 2-((4R)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates

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Synthesis of Methyl 2-((4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates

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Abstract: Chiral oxazolidine moiety is an important core in asymmetric synthesis due to its ability to participate in various stereoselective chemical reactions and because forms a part of more complex important active compounds. Therefore, in this letter we report a convenient diastereoselective and practical strategy for the synthesis of chiral methyl 2-((4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates starting from (*R*)-(–)-2-phenylglycinol and methyl propiolate which were obtained via simple two chemical and stereoselective reactions.

Keywords: asymmetric synthesis; *N*-acryloyl-4-phenyloxazolidine; (*R*)-(-)-2-phenylglycinol; methyl propiolate

1. Introduction

Oxazolidines are five-membered heterocycles that contain an oxygen and nitrogen atom in the 1,3 positions[1]. Chiral oxazolidines are moieties in biologically active compounds [2] and as intermediates materials in the asymmetric synthesis of various compounds [3,4]. Additional, chiral oxazolidines have been used as catalysts [5,6] and as possible drugs [7,8].

Oxazolidines are mainly synthesized by the reaction of an amino alcohol with an aldehyde or a ketone, however, there are more synthetic methods to obtain them[9,10]. Particularly functionalized chiral oxazolidines are compounds for which efforts have been made to obtain stereoselectively [11,12].

In this sense, Agami and coworkers in 2002 reported the synthesis of methyl 2-((4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetate in a yield of 38% as a byproduct of an attempted aza-annulation reaction between a b-enaminoester derived from (*R*)-(-)-2-phenylglycinol and acryloyl chloride [13]. They argued that the poor performance of oxazolidine was due to the trimerization of the corresponding b-enaminoester.

Considering of the above, in this communication we report a straightforward methodology for synthesizing specifically these methyl 2-((4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates as main intermediates.

2. Results

2.1. Synthesis of Chiral Acrylamides

In this synthesis to access methyl 2-(4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates, we begin with the preparation of the respective chiral acrylamides **4** and **5,** through condensation reaction of (*R*)-(-)-2-phenylglycinol **1** and the corresponding acryloyl chlorides **2** or **3**, in a biphasic system CH_2Cl_2:H_2O (1:1), with K_2CO_3, r.t. by 2 h (completion of the reaction monitored by TLC) [14]. Chiral

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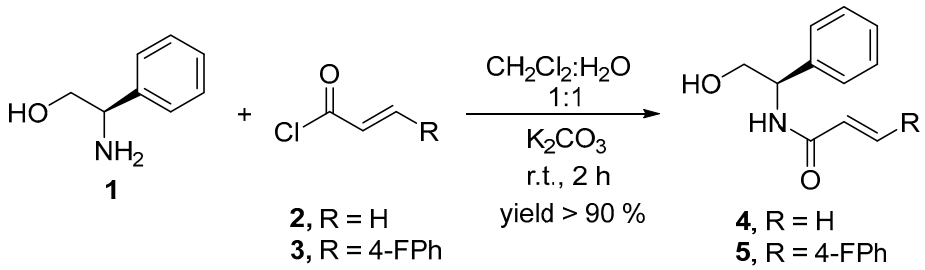
acrylamides **4** and **5** were obtained in yields greater than 90% after purification by column chromatography SiO_2 (Scheme 1).

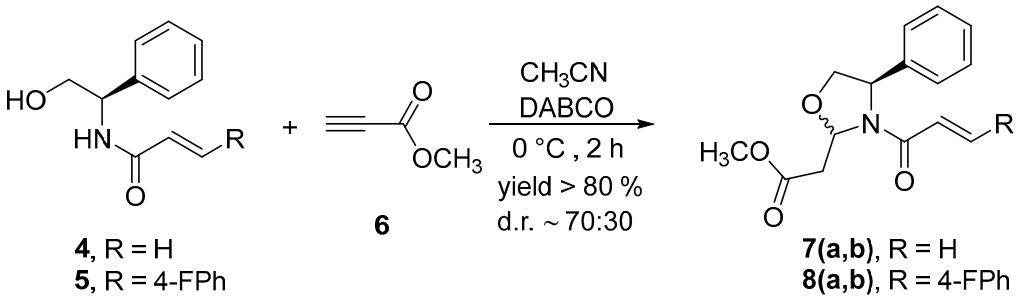


Scheme 1. Synthesis of chiral acrylamides **4** and **5**.

Compounds **4** and **5** were successfully characterized by ^{1}H and ^{13}C NMR spectra. Those spectrums show respectively the characteristic signals for the vinyl H, for **4** at 5.7 ppm(d, J = 11.5 Hz), 6.12 ppm(dd, J = 10.5, 17.0 Hz), and 6.29 ppm (d, J = 15.5 Hz), for **5** at 6.39 ppm (d, J = 15.5 Hz), and 7.60 ppm (d, J = 15.5 Hz). On the other hand, in the ^{13}C NMR spectra, the signal corresponding to the carbonyl group can be observed at 166.0 ppm for **4** and 166.3 ppm for **5** (please refer to the supplementary material).

2.2. Synthesis of Methyl 2-(4R)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates, 7 and 8

The next step was the condensation reaction between the chiral acrylamides and methyl propiolate **6**. To a stirred solution of the corresponding acrylamide in acetonitrile at 0°C, DABCO (10 m0l%) was added. Subsequently, methyl propiolate was added drop by drop [15]. The reaction mixture was kept stirring for an additional 2 h. After purification by column chromatography of the reaction crude, we obtained the chiral oxazolidines **7** and **8**, in yields greater than 80% and *d.r.* around 70:30.



Scheme 2. Synthesis of chiral 4-pheniloxazolidines **7(a,b)** and **8(a,b)**.

The diastereomeric ratio for each 4-phenyloxazolidine **7(a,b)** and **8(a,b)** was determined in the NMR ^{1}H spectrum of the crude reaction, with the signal assigned to H-Bn. The spectrum of diastereomeric mixture of **7(a,b)** shows two signals appearing at 4.34 ppm(dd, J = 6.5, 8.5 Hz) for the major diastereoisomer, and at 4.47 ppm(dd, J = 6.0, 8.5 Hz), for the minor diastereoisomer, yielding a *d.r.* = 74:26. On the other hand, the spectrum of the diastereomeric mixture of **8(a,b)** shows signals at 4.37 ppm (dd, J = 6.5, 9.0 Hz) for the major diastereoisomer, and at 4.51 ppm (dd, J = 6.0, 8.5 Hz) for the minor diastereoisomer, with a *d.r.* = 67:33. Furthermore, in the NMR ^{13}C spectra the signals corresponding to the hemiaminal carbon for each pair of diastereoisomers appear at around 87 ppm (please refer to the supplementary material).

We successfully separated the minor diastereoisomer from mixture **7(a,b)** by using column chromatography (SiO_2, hexane:AcOEt, 70:30). The pure diastereoisomer **7b**, was analyzed by NOESY-

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NMR experiment to determine the relative configuration of the new chiral center generated which was established as 2*S* configuration (Figure 1).

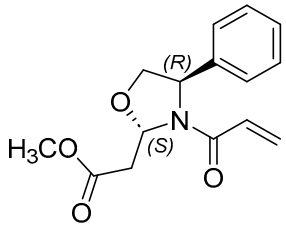

Figure 1. Methyl 2-((2*S*,4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetate, **7b** minor diastereoisomer.

3. Discussion

The condensation of (*R*)-(-)-2-phenylglycinol **1** with acryloyl chlorides **2** and **3** resulted in the formation of chiral acrylamides **4** and **5** in good chemical yields. The reaction was very chemoselective and clean and no byproducts were observed.

In the second step, the condensation of chiral acrylamides **4** and **5** with methyl propiolate **6** was catalyzed with DABCO (10 mol%), maintaining the temperature at 0 °C. This enabled us to obtain the chiral oxazolidines **7(a,b)** and **8(a,b)**, with acceptable diastereomeric relationships. It is important to carry out the reaction at 0 °C because the various reactive sites of methyl propiolate **6** can lead to the formation of byproducts [16].

It should be noted that the ^{1}H NMR analysis of the diastereomeric mixtures did not allow for the assignment of the absolute configuration of the new chiral center. Consequently, the absolute configurations of the major and minor diastereomers could not be determined. Only for the mixture of compound **7(a,b)**, after separating the minor diastereomer **7b** by column chromatography, was it possible to assign the absolute configurations with the aid of the NOESY-NMR experiment. The minor diastereoisomer **7b** was determined to have the (2*S*,4*R*) configuration, and consequently, the major diastereoisomer **7a** was assigned the (2*R*,4*R*) configuration. This same behavior is expected for the mixture of compound **8(a,b)**.

Derived from these results, a plausible mechanism for the catalytic process is described. Initially, an aza-Michael addition reaction of DABCO to chiral acrylamide affords the zwitterionic intermediate in which the Nitrogen nucleophilic character is improving promoting a second aza-Michael addition to methyl propiolate and delivering the high reactive allene which through a proton transfer give an enaminoester. Finally, an oxa-Michael addition reaction followed by a proton transfer produced the desired chiral oxazolidine.

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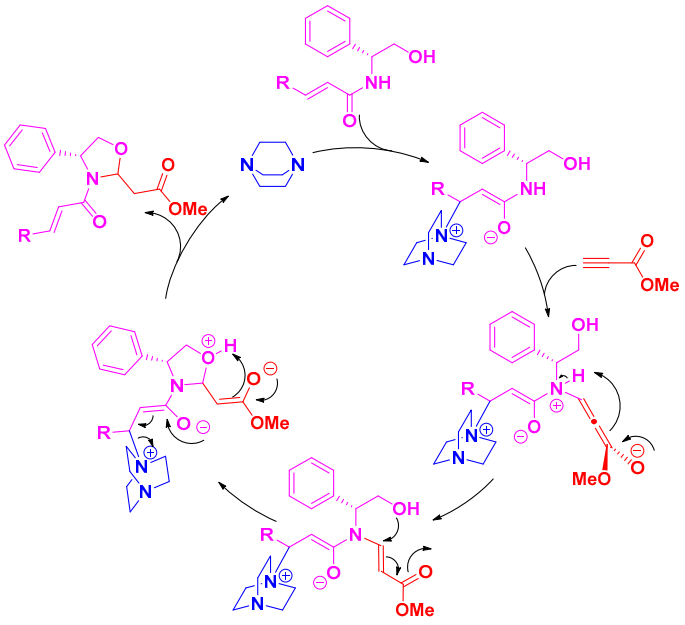

Scheme 3. Mechanistic proposal for the synthesis of *N*-acryloyl-4-phenyloxazolidines.

It is important to note that these highly functionalized oxazolidines have great potential as intermediates in the asymmetric synthesis of piperidine-derived alkaloids

4. Materials and Methods

4.1. General

All commercial reagents and solvents were used without any further purification. NMR spectra were recorded on a 500 MHz Bruker spectrophotometer, with $CDCl_3$ as the solvent and TMS as the reference. Optical rotations were determined at room temperature using a Perkin-Elmer 341 polarimeter, with a 1 dm cell holding a total volume of 1 mL, and reference to the sodium D line. Infrared spectra were obtained using an ATR Perkin-Elmer spectrophotometer. Reactions were monitored by TLC on silica gel 60 F_{254} plates (Merck).

4.2. Synthesis of Chiral Acrylamides

To a solution of (*R*)-(-)-2-phenylglycinol **1** (1.45 mmol) in CH_2Cl_2 (2 mL) was added K_2CO_3 (2.18 mmol) in H_2O (2 mL), then was stirred. After acryloyl chloride, **2** or **3** (2.00 mmol) was added dropwise. The reaction was stirred for 2.0 h at room temperature and monitored by TLC (CH_2Cl_2:MeOH, 95:5). When the reaction ended, extractions were carried out with CH_2Cl_2 (3 x 15 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered, and subsequently the solvent was concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2:MeOH, 80:20).

(*R*)-*N*-(2-Hydroxy-1-phenylethyl)acrylamide **4** in 90% yield as white solid, melting point 120-123 °C, $[a]_D^{20}$ -119.0 (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.88 (d, *J* = 5.0 Hz, 2H-CH_2), 5.10 (dd, *J* = 5.5, 12.5 Hz, 1H-Bn), 5.66 (d, *J* = 11.5 Hz, 1H-CH_2), 6.12 (dd, *J* = 10.5 Hz, 17.0 Hz, 1H-CH), 6.29 (d, *J* = 15.5 Hz, 1H-CH_2), 6.51 (d, *J* = 7.0 Hz, 1H-NH), 7.26 (m, 5H-Ph) (Figure S1). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 56.0, 66.4, 126.8, 127.4, 128.0, 128.9, 130.4, 138.8, 166.0 (Figure S2). IR: 1537, 1626, 3307 cm^{-1} (Figure S3).

(*R*,*E*)-3-(4-Fluorophenyl)-*N*-(2-hydroxy-1-phenylethyl)acrylamide **5** in 85% yield as white solid, melting point 157-160 °C, $[a]_D^{20}$ +19.4 (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.91 (s, 1H-OH), 3.93 (m, 2H-CH_2), 5.19 (dd, *J* = 6.0, 11.0 Hz, 1H-Bn), 6.39 (d, *J* = 15.5 Hz, 1H-CH), 6.43 (d, *J* = 7.0 Hz, 1H-NH), 7.03 (t, *J* = 8.5 Hz, 2H-Ar), 7.30 (m, 5H-Ph), 7.45 (dd, 5.5, 9.0 Hz, 2H-Ar), 7.60 (d, *J* = 15.5

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Hz, 1H-CH) (Figure S4). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 56.3, 66.8, 115.9, 116.1 119.8, 126.8, 128.1, 129.0, 129.7, 129.8, 130.8, 138.7, 140.8, 166.3 (Figure S5). IR: 698, 1224, 1657, 3308 cm^{-1} (Figure S6).

4.3. Synthesis of Methyl 2-(4R)-3-acryloyl-4-phenyloxazolidin-2-yl)acetates

To a solution of chiral acrylamide, **4** or **5** (3.5 mmol) in CH_3CN (10 mL) at 0°C was added DABCO (10 mol%) in CH_3CN (2 mL), and the mixture was stirred. Then, methyl propiolate **6** (5.26 mmol) was added dropwise. The reaction was stirred for 2.0 h at 0°C and monitored by TLC (SiO_2, CH_2Cl_2:MeOH, 95:5). When the reaction ended, the solvent was evaporated under reduced pressure. Then, the mixture was purified by column chromatography (SiO_2, Hexane:AcOEt, 70:30).

Methyl 2-((4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetate **7(a,b)** in 86 % yield as a yellow pale oil, d.r. 74:26. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.72 (m, H-CH_2), 3.31 (d, *J* = 15.5 Hz, 1H-CH_2), 3.44 (d, *J* = 15.0 Hz, 1H-CH_2), 3.73 (s, H-OMe), 3.95 (d, *J* = 9.0 Hz, 1H-CH_2), 4.06 (dd, *J* = 3.0, 8.5 Hz, 1H-CH_2), 4.34 (dd, *J* = 6.5, 8.5 Hz, 1H-Bn), 4.48 (d, *J* = 6.0, 8.5 Hz, 1H-Bn), 5.02 (m, 1H-CH_2), 5.48 (dd, *J* = 2.0, 10.5 Hz, 1H-CH_2), 5.58 (d, *J* = 10.0 Hz, 1H-CH_2), 5.88 (d, *J* = 7.5 Hz, 1H-CH_2), 6.05 (dd, *J* = 10.5, 17.0 Hz, 1H-CH), 6.15 (dd, *J* = 2.5, 8.0 Hz, 1H-CH_2), 6.25 (d, 16.5 Hz, 1H-CH_2), 6.36 (d, *J* = 17.0 Hz, 1H-CH_2), 7.21 (m, H-Ph) (Figure S7). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 37.4, 38.9, 51.9, 52.0, 60.3, 60.3, 73.7, 74.0, 87.8, 88.0, 125.8, 125.9, 128.2, 128.4, 128.6, 129.2, 129.2, 129.4, 139.9, 141.3, 163.7, 165.1, 170.1, 170.3 (Figure S8). IR: 699, 1423, 1649, 1735 cm^{-1} (Figure S9).

Methyl 2-((4*R*)-3-((*E*)-3-(4-fluorophenyl)acryloyl)-4-phenyloxazolidin-2-yl)acetate **8(a,b)** in 81 % yield as a yellow pail oil, d.r. 67:33. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.77 (dd, *J* = 8.5, 16.0 Hz, H-CH_2), 3.34 (dd, *J* = 3.0, 16.0 Hz, 1H-CH_2), 3.46 (d, *J* = 15.5 Hz, 1H-CH_2), 3.74 (s, 3H-OMe), 3.75 (s, 3H-OMe), 3.93 (d, *J* = 5.0 Hz, 1H-CH), 3.99 (dd, *J* = 2.0, 9.0 Hz, 1H-CH_2), 4.08 (dd, *J* = 4.0, 9.0 Hz, 1H-CH_2), 4.37 (dd, *J* = 6.5, 8.5 Hz, 1H-Bn), 4.51 (dd, *J* = 6.0, 8.5 Hz, 1H-Bn), 5.09 (m, H-CH_2), 5.95 (d, *J* = 7.0 Hz, 1H-CH), 6.19 (dd, *J* = 3.0, 8.0 Hz, 1H-CH), 6.25 (d, *J* = 7.5 Hz, 1H-CH_2), 6.05 (dd, *J* = 10.5, 17.0 Hz, 1H-CH), 6.15 (dd, *J* = 2.5, 8.0 Hz, 1H-CH_2), 6.25 (d, 15.5 Hz, 1H-CH), 6.30 (d, *J* = 15.0 Hz, 1H-CH), 6.46 (d, *J* = 15.5 Hz, 1H-CH), 6.93 (m, H-Ph), 7.18 (m, H-Ar), 4.27 (m, H-Ph) (Figure S10). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 37.5, 39.0, 51.9, 52.0, 56.1, 60.4, 60.6, 66.4, 73.7, 74.1, 87.9, 88.1, 115.8, 115.8, 115.8, 115.9, 116.0, 116.0, 118.0, 118.6, 120.3, 120.3, 139.2, 140.0, 140.2, 141.3, 141.4, 142.1, 162.5, 162.6, 162.7, 164.0, 164.5, 164.6, 164.7, 165.4, 166.2, 170.2, 170.3 (Figure S11). IR: 700, 1508, 1650, 1734 cm^{-1} (Figure S12).

Methyl 2-((2*S*,4*R*)-3-acryloyl-4-phenyloxazolidin-2-yl)acetate **7b**, $[a]_D^{20}$ -49.5 (*c* 0.5, CH_2Cl_2).. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.72 (dd, *J* = 8.5, 16.0 Hz, 1H-CH_2), 3.32 (dd, *J* = 2.5, 15.5 Hz, 1H-CH_2), 3.75 (s, 3H-OMe), 3.96 (dd, *J* = 2.5, 9.0 Hz, 1H-CH_2), 4.47 (dd, *J* = 6.0, 9.0 Hz, 1H-Bn), 5.00 (d, *J* = 6.5 Hz, 1H-CH_2), 5.47 (d, *J* = 10.5 Hz, 1H-CH_2), 6.04 (dd, *J* = 10.5, 16.5 Hz, 1H-CH), 6.15 (dd, *J* = 3.0, 8.0 Hz, 1H-O-CH-N), 6.26 (d, *J* = 16.5 Hz, 1H-CH_2), 7.21 (5H-Ph) (Figure S13). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 29.7, 37.4, 51.9, 60.3, 73.7, 88.0, 125.8, 128.2, 128.5, 128.6, 129.1, 141.3, 163.7, 170.2 (Figure S14). See COSY and NOESY spectra in Figures S14 and S15 respectively.

5. Conclusions

In this communication, we report a simple two-step synthesis of two *N*-acryloyl-4-phenyloxazolidines **7(a,b)** and **8(a,b)** from chiral acrylamides **4** and **5** derived from (*R*)-(-)-2-phenylglycinol **1** and their condensation with methyl propiolate **6**. These compounds were obtained in good chemical and stereochemical yields as mixtures of diastereoisomers. The minor diastereoisomer of compound **7b** was purified, and the absolute configuration was assigned as (2*S*,4*R*).

Supplementary Materials: IR and NMR spectra of compounds are available online at preprints.org.

Author Contributions: Conceptualization, H.P.X; performing synthesis, J.G.O.M; investigation, D.H.G.M; resources, M.L.O.F. and D.H.G.M; writing—original draft preparation, H.P.X.; review and editing, J.L.T.V and E.H.N.; supervision, M.L.O.F. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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