**Diastereoselective Synthesis of somes**

**pyrrolidin-2-ones azasugars and study of their stereochemistry**

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To the memory of Dr: Aloysius Siriwardena

**Abstract:**

The microwave-promoted one-pot multicomponent synthesis of substituted pyrrolidinols using a pool O-isopropylidene-D-erythruronolactone as masked aldehyde acide and different nucleophiles is reported. Clean reaction profile, easy work-up procedure, excellent yields and short reaction times are some remarkable features of this method. We have also studied the stereochemistry of our pyrrolidinols and the influence of nucleophiles on our initial reactive

This strategy highly viable for future applications for synthesis of derivatives indolizidine

**Keywords**

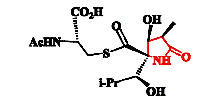
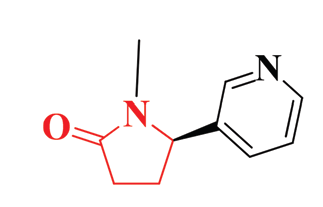
Microwave, Pyrrolidinone, One pot, Multicomponent, Organic reaction, Diastereselective.

1. **Introduction**

Multicomponent reactions (MCR) take advantage of creating and transforming reactive functionalities in the same reaction vessel without intermediary work-up.[1], [2].

MCRs based on the synthesis of heterocyclic compounds containing a 2-pyrrolidinone gained much importance in organic synthesis. 2-Pyrrolidinones are important compounds that are found in many pharmaceuticals and in active natural products (Fig. 1). [3].

Pyrrolidinone is a five membered heterocyclic ring that is a versatile lead compound for designing powerful bioactive agents.



1. **2**

**Figure1:** Selected compounds with a 2-pyrrolidinone moiety.

Some of them are well known medicines, such us piracetam **3** for patients with seizures, Alzheimer’s, and other neurological problems [4], doxapram **4** for patients with respiratory failure *etc.* [5]. (Figure 2)



**3 4**

**Figure 2**: Structure of piracetam and doxapram

In view of the importance of substituted pyrrolidinones, many procedures for the preparation have been developed offer wide spans in the field of medicinal chemistry. [6], [7]

Considering the importance of clean chemistry, in this study we have developed a methodology for the synthesis of substituted pyrrolin-2-ones without solvent under microwave irradiation. The key of the strategy used a multicomponent reaction to assemble one-pot aldehyde and an acid with a primary amine or other.

1. **Results and discussion**

We reporte the synthesis of pyrrolidinols from 3-O-isopropylidene-D-erythruronolactone, oxidative cleavage and double nucleophilic displacement as the key steps. The method demonstrates high diastereoselectivities at the 2-pyrrolidinone ring (C-4/C-5).

We planned the synthesis of the pyrrolidinols and the study of some interesting phenomena such as a remarkable difference in reactivity of 2,3-O-isopropylidene-D-erythruronolactone towards the condensation reactions with different nucleophiles (scheme 1).

The effect of microwave irradiation in accelerating the reactions attracted our attention. Micro wave irradiation has widely used among synthetic organic chemists to improve classical organic reactions, shorting reaction times and/or improving yields, as well as promoting new reactions [8].



Scheme 1: Synthesis of substituted pyrrolidinols .

To achieve suitable conditions for the synthesis of substituted pyrrolin-2-ones **(5** and **6)**, various reaction conditions were investigated. We first optimized the reaction conditions, such as the effects of solvents, the quantity of nucleophile and micro wave irradiation power.

After finding a suitable solvent (CH2Cl2) and power (14W) to determine the important role of microwave ,this method was examined with the reaction of different nucleophile and the pool 2,3-O-isopropylidene-D-erythruronolactone in dichloromethane solvent under microwave irradiation and without microwave irradiation at room temperature (Table 1).

As shown in Table 1, when the reactions were carried out with the conventional method, these took a comparatively longer time and resulted in lower yields; whereas when the same reactions were performed under the influence of microwave conditions, they gave higher yields in shorter reaction times. Generally, a similar effect was seen in all reactions, and

We found that microwave irradiation was very effective and useful in our work, because the products could be synthesized in a short time with excellent yields.

The method remains effective because it is carried out in a single step, especially since the glyco-α-amino-nitriles described in the literature are synthesized according to several stages. [09].

The 2,3-O-isopropylidene-D-gulonolactone derivative was synthesized from D-gulunolactone **95**% yield by the procedure described by Borcherdinf et all. [10]

Table 1: *Comparison of the times and yields of the reactions with or without irradiation for the synthesis of substituted pyrrolidinols*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | R | Product with rapport (**α/ β)** | With  irradiation | Without  irradiation |
| Time (min) Yield (%) | Time (min) Yield (%) |
| 1 | Cyano-mehtyl | **5a 5b**  **(α/ β)= 25/75** | 20 80 | 720 70 |
| 2 | 2-Azidoethyl | 5**c 5d**  **(α/ β)= 25/75** | 20 70 | 720 44 |
| 3 | Pyridin-2yl | **6 a 6b**  **(α/ β)= 25/75** | 25 45 | 720 17 |
| 4 | Phenyl | **6c 6d**  **(α/ β)= 25/75** | 25 40 | 720 12 |
| 5 | Ethyl | **6e 6f**  **(α/ β)= 25/75** | 25 50 | 720 30 |

The suggested mechanism for the synthesis of substituted pyrrolidinols (5 and 6 ) is illustrated in Scheme 2. That the first step in the reaction may proceed via formation of the imine . This is activated by intramolecular protonation to lead to a more electrophilic iminium (I.1). The nucleophile or nitrogen atom of excess of amine adds up on the electrophilic iminium, thus forming the intermediate (I.2), then the intermediate (I.3) is formed, after attack of the carbonyl by the doublet of nitrogen (I.4) and elimination of a molecule of water, pyrrolidine is formed.



Scheme 2 : *Proposed mechanistic path for the synthesis of substituted pyrrolidinols (4a–j).*

Reaction yield is satisfactory passing from 40 to 80 yields, and good diastereoselectivities were obtained (**25:75 dr**).

The configuration at the epimeric center was assigned on the base of their spectroscopic properties. The stereochemistry of compounds 5a-d (and 6 a-f) deserves comment.

The aim is to establish without ambiguity the stereochemistry (cis, trans) of epimers tentatively noted α and β.

• The first point to note is the configuration retention of carbons 3 and 4. This configuration of the two carbons C-3 and C-4 is known since they are obtained from precursors whose geometry is perfectly established 3J (cis) ~ 6Hz.

• The second point is the assignment of the δ of the different protons in the two epimers. This point has been clearly elucidated using correlation NMR. The study of the HETCOR spectra of pairs of epimers7a makes it possible to produce the following table:

**Table 2:** *Correlations observed on the HSQC spectra for the compound* ***5a/b***

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Epimer α (5a)** | | | | **Epimer β (5b)** | | | |
| **Ci** | **δ (ppm)** | **Hi** | **δ (ppm)** | **Ci** | **δ (ppm)** | **Hi** | **δ (ppm)** |
| C3 | 77.02 | H3 | 4.62- 4.65 | C3 | 78.07 | H3 | 4.51-4.60 |
| C4 | 73.18 | H4 | 4.75- 4.80 | C4 | 76.94 | H4 | 4.49-4.51 |
| C5 | 73.24 | H5 | 4.45-4.51 | C5 | 76.15 | H5 | 4.75 |

From this attribution corresponding to the two epimers, the measure of *J* should allow the distinction between the forms α and β.

A stereochemical study of analogous heterocycles is mentioned in the literature. In the first example Zhou and al. While the vicinal coupling constants (*J*4,5>6.0 Hz) for cis-diastereomers **8** and *J*4,= 0–4.4 Hz for trans-diastereomers **7**, (example 1) are commonly used to determine the 4,5-relative stereochemistries of 4,5-disubstituted δ-lactams. [11].



**Example 1**: *Attribution of stereochemistry according to Zhou*

In the second example Pinhey et al. show that the coupling constant for the cis isomer is greater than that of the trans isomer.[12].



**Example 2:** *Attribution of stereochemistry according to Zhou*

Stereochemistry is progressively assigned by studying the different couplings of the cyclic protons.

• **3*J*34:** The relative configuration of carbons 3 and 4 is well known, it is identical for both epimers. The measurement of the 3*J***34** coupling constant is of the order of 6 Hz. This result is also confirmed in example 2.

**• 3*J*45:** The stripping of the 1H NMR spectra of heterocyclic compounds **5** and **6** proves very delicate because of the proximity of the signals of the different cyclic hydrogens and the numerous couplings. All the hydrogens resonate in a range of 1 ppm between 4 and 5 ppm. It is known that the shape of an H NMR spectrum depends on the evaluation of the Δν / *J* ratio. Indeed, the small value of the differences in resonant frequencies with respect to the coupling constant *J* complicates the appearance of the spectra.

• It is noted that the proton H-5 appears in the form of a doublet due to the coupling with H-4 in the compounds α, against in series β, it is in singlet, which indicates that the coupling with H-4 disappears (scheme 3). This result is not surprising since the constant J depends on the dihedral angle of the two coupled protons. The same phenomenonis observed in Example 2 (*J*7.11 = 0 Hz).



**Scheme 3:** *Assignment of the stereochemistry of α and β compounds.*

Very low or even zero coupling constants indicate dihedral angles between 90 ° and 100 °. In addition it is known that the pyrrolidinone ring is not plane, it can exist in enveloped forms



**Scheme 4:** *The two possible enveloping forms of pyrrolidinone*

This is the case of the epimer β which has a 3*J*4.5 = 0 Hz. 4.5 would be close to 100 ° it is attributed the configuration Trans. (as seen in figure I, scheme 5).

The coupling constant 3*J*4.5 = 6 Hz implies dihedral angles θ4.5 ~ 20-30 °. The same caution must be pointed out, these are very approximate values, this is the case of the epimer α (3J4.5 = 6 Hz with θ 4.5 = 30 °), it is assigned the Cis configuration (as seen in Figure II, scheme 5).

The differences between the measured 3*J*4.5 and the approximate values of the dihedral angles are large enough to allow correct assignments

**Figure I Figure II**

**Scheme 5:** *Representation in the space of epimers α and β*

The next step of this work, we introduced different nucleophiles to test the reactivity of 2,3-O-isopropylidene-D-erythruronolactone (Scheme 6). However, the difficult of separation have reduced the yield of isolated product. At the end of the reaction, we obtain four products difficult to separate by column. We conclude that it is difficult to control the reactivity of iminium ions. The same diastereoselectivity has been observed for additions of nucleophic reagents to 2,3-O-isopropylidene-D-erythruronolactone dr (25:75).

In all three cases, complex mixtures (TLC analysis) are obtained which are difficult to separate. However, the desired products have been isolated but with low yields, (Scheme 6).

The compounds **10a,bc,d** are characterized by mass spectroscopy , peaks m/z = 305 and m/ z = 353 correspond to the proton form of the molecular peak MH +.



Scheme 6: *Synthesis of pyrrolidinols with non-identical spacer arms*

1. **Conclusion**

In this work, the reported method offers a simple and efficient route for the one-pot microwave chemical synthesis of substituted pyrrolidnols. Some important superiorities of this method are its short reaction time, without solvent, easy work-up, high yields.

1. **Experiment**

The CEM Discover microwave allows irradiating in two modes: either an assigned power with continuous measure of the resulting temperature by an IR captor or an assigned temperature with continuous adjustment of the irradiation power. We chose the second mode, in solvent-free conditions with assigned temperature to avoid degradation of sugars by browning reactions. Chemicals were purchased from Aldrich, Acros and Fluka and used without further purification. Solvents distilled with appropriate drying agents. All reactions performed under anhydrous conditions employing routine drying techniques unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) performed on E. Merck glass plates silica gel sheets (Silica Gel F254) and stained with vanillin acid-aqueous H2SO4 solution. Column chromatography carried out on silica gel (E. Merck 230-400 mesh). Nuclear Magnetic Resonance (NMR) data (1H or 13C) were obtained on a AC-Brucker 300 machine chemical shifts are reported in parts per million relative to tetramethylsilane in deuterated solvents. Assignments of 1H and 13C were assisted by 2D 1H COSY and 2D

1H– 13C CORR experiments.Optical rotations were determined with a Jasco Dip 370 electronic micropolarimeter (10 cm cell). High-Resolution Electro spray Mass Spectra (ESI-HRMS) in the positive ion mode were obtained on a Q-TOF *Ultima* *Global* hybrid quadrupole time-of-flight instrument (Waters-Micro mass), equipped with a pneumatically assisted electro spray (Z-spray) ionization source and an additional sprayer (Lock Spray) for the reference compound.

**4.1. General Procedure for Synthesis of (5 a-d).**

To a mixture of 2,3-O-isopropylidene-D-erythruronolactone (0.86 mmolof sugar) and a primary amine (excess) 5mL of CH2Cl2 was added. The mixture was stirred for 12 h at rt. After concentration under reduced pressure, the resulting was purified by chromatography (CH2Cl2/MeOH, 95/5). The characterization of each compound was obtained by means

of NMR and mass spectrometry as reported below.

* 1. **.Synthesis of substituted pyrrolidinols 5 a-d under microwave irradiation**

A mixture of 2,3-O-isoproprylidene-D-erythruronolactone (0.86 mmol of sugar) and primary amine (excess) were thoroughly mixed in an open Pyrex flask. The flask placed in the MW reactor (CEM Discover) and irradiated. After irradiation, the crude reaction mixture was cooled down to room temperature and solvent of CH2Cl2 (20 ml) was added, the resulting mixture was concentrated in vacuum, purified by chromatography (CH2Cl2/MeOH, 95/5).

*N-1-(3-cyanoethylamino)-3,4-O-isopropylidendioxy-5-(3-cyanoethylamino)-pyrrolidin-2-one* ***5 (a-b****).* These compounds were obtained as a mixture of epimers non-separable by chromatography, colorless syrup.

For the epimer **(5a)**, NMR 1H (300 MHz, CDCl3)**:** δ4.75-4.80 (m, 1H, H-4), 4.62-4.65 (d, *J*=3.1 Hz, 1H, H-3); 4.45-4.51 (d, *J*=2.08 Hz , 1H, H-5), 3.6-3.7 (m, 2H, CH2-N); 3.1-3.2 (m, 1H, CH2-CH2CN); 2.98-3.1 (m, 1H, CH2-CH2CN); 2.7-2.8 (m, 2H, CH2CH2CN); 2.1 (s, 6H); 2.5 (m, 2H; CH2CN). NMR 13C (75 MHz, CDCl3)**:** δ169.88 (C=O); 12.61-112.77; 73.18-73.24;77.02; (C-N3);48.40-49.03; 37.09-40.71; 27.04-29.38; 25.53-27.04.

For the epimer **(5b ).** NMR 1H ( 300 MHz, CDCl3)**:** δ4.75- (s, 1H, H-5); 4.51-4.60 (d, *J*=2.07 Hz, 1H, H-3); 4.49-4.51 (m, *J*=2.01 Hz , 1H, H-4); 3.6-3.7 (m, 2H, CH2-N); 3.1-3.2 (m, 1H, CH2-CH2CN); 2.98-3.1 (m, 1H, CH2-CH2CN); 2.7-2.8 (m, 2H, CH2CH2CN); 2.5 (m, 2H; CH2CN); 2.1 (s, 6H, CH3).NMR 13C (75 MHz, CDCl3):δ170.98 (C=O), 112.61-112.77; 78.07; 76.94; 76.15; 48.40-49.03 (C-N3); 37.39-43.75; 27.04-29.38; 25.53-27.04.

HRMS (m/z) [M+Na]+calcd for C13H23N8O3 [M+H] + 339.1893 found 339.1886.

*N-1-(3-azidopropyl)-3,4-O-isopropylidendioxy-5-(3-azidopropylamino)-pyrrolidin-2-one* ***5 (c-d****).* These compounds were obtained as a mixture of epimers non-separable by chromatography, colorless syrup.

For the epimer **(5c)**, NMR 1H ( 300 MHz, CDCl3)**:** δ4.71-4.73(m, 1H, H-4); 4.56-4.58 (d, *J*=5.61 Hz, 1H, H-3); 4.27-4.29 (d, *J*=4.60 Hz , 1H, H-5); 3.27-3.38 (m, 4H, CH2-N3); 3.51-3.55 (m,1H, CH2 ); 3.09-3.13 (m, 1H, CH2); 2.60-2.64 (m, 1H, CH2 ); 2.49-2.53 (m, 1H, CH2); 1.21-1.75 (m, 4H; CH2); 1.38-1.53 (s, 6H, CH3). NMR 13C (75 MHz, CDCl3)**:** δ169.88 (C=O);12.61-112.77; 73.18, 73.24;77.02; (C-N3);48.40-49.03; 37.09-40.71; 27.04-29.38; 25.53-27.04.

For the epimer **(5d ).** NMR 1H (300 MHz, CDCl3):δ4.65-4.67 (d, *J*= 5.92 Hz ,1H, H-4); 4.43-4.45 (d, *J*=5.04 Hz ,1H, H-3); 4.34 (s, 1H, H-5); 3.27-3.38 (m, 1H, CH2, 4 H, CH2-N3 ); 2.88-2.94 (m, 1H, CH2); 2.64-2.73 (m, 1H, CH2); 1.21-1.75 (m, 4H; CH2); 1.38-1.53 (s, 6H, CH3). NMR 13C (75 MHz, CDCl3):δ170.98 (C=O), 112.61-112.77; 78.07; 76.94; 76.15; 48.40-49.03 (C-N3); 37.39-43.75; 27.04-29.38; 25.53-27.04.

HRMS (m/z) [M+Na]+ calcd for C13H23N8O3 [M+H] + 339.1893 found 339.1886.

* 1. **. Representative procedure for synthesis of 6(a-f):**

To a mixture of 2,3-O-isopropylidene-D-erythruronolactone (0.86 mmol of sugar) and 1.2 eq of amine, 5mL of CH2Cl2 was added, after 10 minute of reaction , trimethylsilyl cyanide was added . The mixture was stirred for 12 h at room temperature.

After concentration under reduced pressure, the resulting was purified by chromatography (EtOAc /cyclohexane, 70/30).

* 1. **.Synthesis of substituted pyrrolidinols 6(a-f) under microwave irradiation**

A mixture of 2,3-O-isoproprylidene-D-erythruronolactone (0.86 mmol of sugar) and primary amine (1.2) were thoroughly mixed in an open Pyrex flask. The flask placed in the MW reactor (CEM Discover) and irradiated for 10 mn. Trimethylsilyl cyanide was added . The mixture was irradiated for 15 mn. After concentration under reduced pressure, the resulting was purified by chromatography (EtOAc /cyclohexane, 70/30).

*( Pyridin-2-yl-methyl)-3,4-O-isopropylidendioxy-5-(cyano)-pyrrolidin-2-one (****6* a-*b)***

These compounds were obtained as a mixture of epimers non separable by chromatography, yellow gum.

For epimer **6 a**. NMR 1H (300 MHz, CDCl3):δ7.28-7.41(m, H-aromtic). 5.29-5.34 (d, *J*= 14.69 Hz, 1H, CH2);4.82-4.84 (m, *J*= 5.48 Hz ,1H, H-4); 4.75-4.77 (d, *J*= 6.14 Hz ,1H, H-3); 4.33-4.35 (d, *J*=5.27 Hz, 1H, H-5); 4.03-4.08 (d, *J*= 14.24 Hz, 1H, CH2); 1.56 (s, 3H); 1.65 (s, 3H). NMR 13C (75 MHz, CDCl3):δ168.18 (C=O); 114.17-114.94 (CN); 112.9; 77.26; 71.25; 51.46-51.58; 45.50-45.58; 25.87-26.94.

For epimer **6 b.** NMR 1H (300 MHz, CDCl3):δ7.28-7.41(m, H-aromtic); 5.21-5.26 (d, *J*= 14.69 Hz, 1H, CH2); 4.91 (m, 2H, H-4, H-3); 4.18 (s, 1H, J= 0 Hz, H-5); 4.05-4.08 (d, *J*= 14.91 Hz ,1H, CH2); 1.29-1.48 (2s, 6H). NMR 13C (75 MHz, CDCl3):δ168.76 (C=O); 114.17-114.94 (CN); 112.9; 76.89; 74.97; 51.46-51.58; 45.50-45.58; 25.87-26.94.

HRMS (m/z) [M+Na]+ calcd for C14H15N3O3Na : 269.1011 found 296.1019 .

*( Benzyl)-3,4-O-isopropylidendioxy-5-(cyano)-pyrrolidin-2-one:* ***6(*c-*d)***

These compounds were obtained as a mixture of epimers non separable by chromatography, yellow gum.

For epimer **6 c.** NMR 1H ( 300 MHz, CDCl3):δ7.28-7.41(m, H-aromtic); 5.29-5.34 (d, *J*= 14.69 Hz ,2H, CH2); 5.23-5.29 (d, *J*= 16.22 Hz, 2H, CH2); 4.93-4.96 (m, *J*= 3.73 Hz ,1H, H-4); 4.81-4.83 (m, 2H, H-3, H-5); 1.60 (s, 3H); 1.70 (s, 3H). NMR 13C (75 MHz, CDCl3):δ 168.18 (C=O); 114.74 (CN); 113.43; 77.26; 71.25 ; 51.46-51.58; 45.50-45.58; 25.87-26.94

For the epimer **6 d**. NMR 1H ( 300 MHz, CDCl3):δ8.53-8.59 (m, H-aromtic). 7.69-7.72 (m, H-aromtic); 7.25-7.34 (m, H-aromtic); 5.07-5.11 (d, *J*= 12.00 Hz, 1H, CH2); 4.93-4.96 (m, *J*=3.73 Hz ,2H, H-4, H-3); 4.08 (d, *J*= 1.32 Hz , 1H, H-5); 4.32-4.39 (dd, , *J*′= 15..53 Hz , 4.82 Hz, 1H, CH2); 1.42-1.43 (s, 3H, CH3); 1.35 (1s, 3H, CH3). NMR 13C (75 MHz, CDCl3):δ170.17 (C=O). 149.72 (C-aromatic); 137.16 (C-aromatc); 122.78-123.23 (C-aromatic); 115.38 (CN); 114.23; 76.59; 75.37; 53.09; 46.80; 26.87-26.96.

**HRMS** (m/z) calcd for C15H16N2O3Na [M+Na] + = 295.1059 found: 295.1053.

*( Propyl)-3,4-O-isopropylidendioxy-5-(cyano)-pyrrolidin-2-one* ***6 (*e-*f)***

These compounds were obtained as a mixture of epimers non separable by chromatography, brown syrup.

For the epimer***6 e****.* NMR 1H (300 MHz, CDCl3):δ4.91-4.93 (m, 1H, H-4); 4.83-4.4.85 (d, *J*= 5.92 Hz, 1H, H-3); 4.66-4.68 (d, *J*= 5.48 Hz, 1H, H-5); 3.63-3.74 (m, 1H, CH2);3.12-3.25 (m, 1H, CH2); 1.59-1.76 (m, 2H, CH2); 1.47 (s, 3H, CH2), 1.49 (s, 3H, CH3); 0.93-1.00 (1s, 3H, CH3). NMR 13C (75 MHz, CDCl3):δ170.29 (C=O); 115.35 (CN); 114.13; 76.87; 75.19; 52.32; 43.54; 25.88-26.98; 19.71; 10.93.

For the epimer **6 f.** NMR 1H (300 MHz, CDCl3):δ4.88-4.90 (d, *J*=5.92 Hz, 1H, H-4). 4.72-4.74 (d, *J*= 6.16 Hz ,1H, H-3); 4.44 (s, 1H); 3.63-3.74 (m, 1H, CH2); 3.12-3.25 (m, 1H,CH2); 1.59-1.76 (m, 2H, CH2 ); 1.56 (s, 3H, CH3), 1.49 (s, 3H); 0.93-1.00 (1s, 3H, CH3). NMR 13C (75 MHz, CDCl3):δ169.66 (C=O); 114.73; 113.29; 77.27; 71.54; 52.44; 43.74; 43.74; 25.88-26.98; 20.15; 11.14.

**HRMS** (m/z) calcd for C11H16N2O3Na [M+Na]+ 247.1059 found: 247.1058.

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