A Facile Route for the Synthesis of Novel γ- Lactams

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A selective reduction and its subsequent cyclisation of novel isoxazolidines into γ-lactams have been examined in presence of Raney - nickel catalyst.

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γ-Lactams are useful synthetic intermediates in organic synthesis. They also play a key role in the treatment of rheumatoid arthritis disease [1]. Several methods have been developed to prepare the γ-lactam ring systems [2]. We previously reported a facile method for the synthesis of a variety of nitrones [3]. Among these, few nitrones were effectively used to prepare biologically interesting N-acetoxy compounds [4]. Recently, our group showed that cycloaddition products of N-substituted nitrones are also antifungal and antibacterials [5]. Nitrones are an attractive class of 1,3-dipoles because of their versatile synthetic applications in organic synthesis. The 1,3-dipolar cycloaddition reactions of nitrones are well documented and provide efficient entries to the synthesis of isoxazolidines [6]. The isoxazolidines are valuable intermediates in organic synthesis and its ring containing biphenylic compounds are more active towards antifungal and antibacterial activity [7]. Literature survey reveals that selected isoxazolidines are also useful precursors for the synthesis of γ-lactams [8].

In the interest of the above, we report a facile and novel route for the synthesis of some biologically active isoxazolidines and its subsequent reductive cyclisation to obtain γ-lactams. The reductive cyclisation process is well established by using Raney-nickel, a catalyst and formic acid as a proton donor in presence of methanolic water (1:1) solvent system.

The nitrones **1a-d** used in this work were prepared according to the procedure reported earlier [1]. Required isoxazolidines, **3a-d** were synthesized by 1,3-dipolar cycloaddition reactions of **1a-d** with ester substituted alkene **2**. Two regioisomers **3a-d** and **4a-d** were obtained is described in Scheme 1. Compounds **3a-d** were found to be the major products with 79-85% and isomers **4a-d** were obtained in 4-6% yield [9]. The course of this reaction was also examined in decalin and found to be effective but isolation of the products was found to be difficult because of its high b.p (189-191 °C). Therefore, all reactions were carried out in xylene/toluene solvent media (Table 1).

Table 1

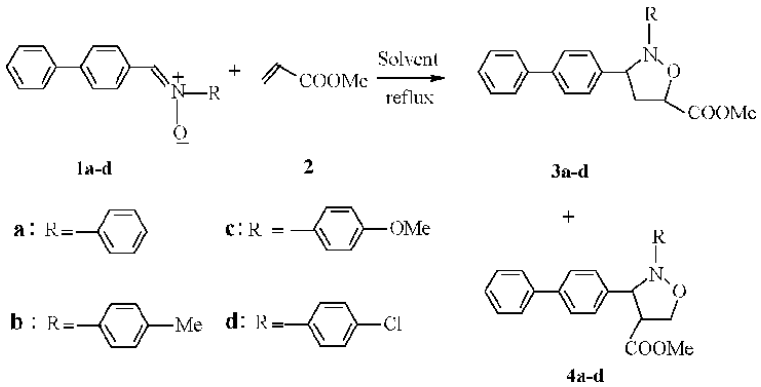
Reaction condition and physical data of theisoxazolidines

Nitrone	Alkene	Solvent Conditions	Time (hrs)	% of Yield[a] **3**	**4**
1a	**2**	Toluene	20	81	4
1b	**2**	Xylene	19	85	6
1c	**2**	Xylene	22	83	4
1d	**2**	Xylene	21	79	3

[a] Purified by column chromatography using hexane-ethyl acetate (1:1) as eluent.

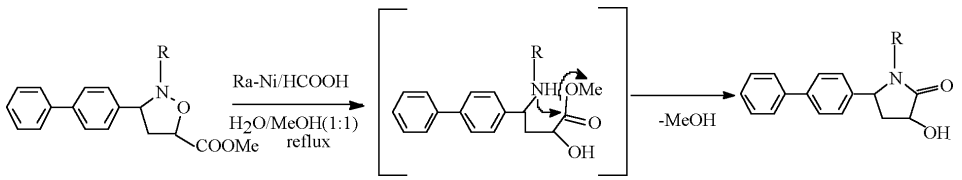
The selective reduction of nitrogen-oxygen bond in isoxazolidines (**3a-d**) and subsequent cyclisation leads to γ-lactams (**6a-d**). This cheaper, non-hazardous and novel synthetic method was achieved by using Raney-nickel and formic acid. A possible mechanism for the reductive

Scheme 1



1,3-Dipolar cycloaddition reactions of nitrone **1a-d** with ester substituted alkene **2**.

Scheme 2



Synthesis of g-lactams **6(a-d)** by Raney-nickel and formic acid reduction of **3a-d**.

cyclisation reaction is depicted in Scheme 2. After performing several experiments, methanol/water (v/v=1:1) or ethanol/water (v/v =2:1) was found to be very effective for γ-lactams formation.

Table 2
Reaction Condition and Yield of the Isoxazolidines

Isoxazolidines	Time (hrs)	γ-Lactams	% of Yield
3a	4.0	**6a**	68
3b	3.7	**6b**	71
3c	3.4	**6c**	65
3d	4.6	**6d**	73

The above reductive cyclisation reaction was carried out by using several solvent systems. Among these, the polar solvent like methanol/water (v/v=1:1) gave the best result (Table 2). The nitrogen-oxygen bond in isoxazolidines **3a-d** was selectively reduced by Raney-nickel catalyzed formic acid and subsequent cyclization into their corresponding γ-lactams with good yield (60-73%). The reduction reaction was also examined with ammonium formate and found to be less effective.

In conclusion, the present method affords several advantages: (I) both the raney nickel and formic acid reagents are readily available and less expensive, and (ii) The method is facile and selective for the synthesis of γ-lactams. A further investigation on the selective reduction of N-O bond in isoxazolidines ring containing sensitive groups is under investigation.

EXPERIMENTAL

Silica gel GF254 and 60 were used for TLC and column chromatography respectively. Starting materials and reagents were obtained from commercial source, such as Aldrich E-Merck and s. d. fine. All melting points were recorded on a SELACO 605 melting point apparatus and uncorrected. IR spectra were recorded on a Bio-Rad Win-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker AMX-400 MHz spectrometer using deuterated chloroform as solvent with tetramethyl silane as internal standard. Elemental analyses were obtained on vario-EL instrument. Nitrones **1a-d** were prepared according to the published procedure [1].

General Procedure for the Synthesis of Isoxazolidines **3a-d**.

An equimolar mixture of nitrone **1a-d** and alkene **2** were dissolved in 10 ml of toluene/xylene and refluxed for 19-22 hrs, and the reaction was monitored by TLC. Pure products were separated on silica gel column chromatography using hexane-ethyl acetate (1:1) as eluent.

Methyl-3-(1,1'-biphenyl-4-yl)-2-phenylisoxazolidine-5-carboxylate (**3a**).

Compound **1a** (1 g, 3.663 mmol) and alkene **2** (0.2564 g, 3.663 mmol) in 10 ml of toluene according to the general procedure resulted in 0.810 g of **3a** obtained as yellow oil; yield 81%; ir (Nujol): 1742 cm^{-1} (C=O); 1702 cm^{-1} (CO); 1280cm $^{-1}$(NO); ^{1}H nmr (deuteriochloroform): δ 2.94 (dd, 2H, CH_2); 3.41 (s, 3H, OCH_3); 4.45 (t, 1H, O-CH); 5.12 (t, 1H, Ar-CH); 6.92 (t, 1H, Ar-H); 7.24 (t, 2H, Ar-H); 7.41 (d, 2H, Ar-H, BP); 7.52 (t, 1H, Ar-H,); 7.64 (t, 2H, Ar-H,); 7.72 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H,).

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.88; H, 5.85; N, 3.9. Found: C, 76.46; H, 5.48; N, 3.72.

Methyl-3- (1,1'-biphenyl-4-yl)-2-(4-methyl)-phenylisoxazolidine-5-carboxylate (**3b**).

Compound **1b** (1 g, 3.484 mmol) and alkene **2** (0.2439 g, 3.484 mmol) in 10 ml of toluene according to the general procedure resulted in 0.853 g of **3b** obtained as yellow oil; yield 85%; ir (Nujol): 1726 cm^{-1} (C=O); 1708 cm $^{-1}$ (CO); 1240 cm $^{-1}$(NO); ^{1}H nmr: (deuteriochloroform): δ 2.28 (s, 3H, Ar-CH_3); 2.67-2.84 (dd, 2H); 3.41 (s, 3H, OCH_3); 4.45 (t, 1H); 5.12 (t, 1H); 6.92 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H); 7.52 (t, 1H, Ar-H); 7.55 (d, 2H, Ar-H); 7.63 (t, 2H, Ar-H); 7.74 (d, 4H, Ar-H).

Anal.Calcd. for $C_{24}H_{23}NO_3$: C, 77.2; H, 6.17; N, 3.75. Found: C, 77.12; H, 6.12; N, 3.58.

Methyl-3- (1,1'-biphenyl-4-yl)-2-(4-methoxy)-phenylisoxazolidine-5-carboxylate (**3c**).

Compound **1a** (1 g, 3.300 mmol) and alkene **2** (0.2310 g, 3.300 mmol) in 10 ml of toluene according to the general procedure resulted in 0.832 g of **3c** obtained as yellow oil; yield 83%; ir (Nujol): 1736 cm^{-1} (C=O); 1758 cm $^{-1}$ (CO); 1240 cm $^{-1}$(NO); ^{1}H nmr: (deuteriochloroform): δ 2.66-2.84 (dd, 2H); 3.43 (s, 3H, OCH_3); 3.81 (s, 3H, Ar-OCH_3); 4.44 (t, 1H); 5.14 (t, 1H); 7.28 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H); 7.52 (t, 1H, Ar-H); 7.63 (t, 2H, Ar-H); 7.68 (d, 2H, Ar-H); 7.74(d, 4H, Ar-H).

Anal. Calcd. for $C_{24}H_{23}NO_4$: C, 74.04; H, 5.91; N, 3.60. Found: C, 74.12; H, 5.69; N, 3.48.

Methyl-3-(1,1'-biphenyl-4-yl)-2-(4-chloro)-phenylisoxazolidine-5-carboxylate (**3d**).

Compound **1a** (1 g, 3.252 mmol) and alkene **2** (0.2276 g, 3.252 mmol) in 10 ml of toluene according to the general procedure resulted in 0.791 g of **3d** obtained as yellow oil; yield 79%; ir (Nujol): 1745 cm^{-1} (C=O); 1762 cm^{-1} (CO); 1278 cm^{-1}(NO); ^1H nmr deuteriochloroform): δ 2.87-3.05 (dd, 2H); 3.41 (s, 3H, OCH_3); 4.44 (t, 1H); 5.15 (t, 1H); 7.28 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H); 7.52 (t, 1H, Ar-H); 7.64 (t, 2H, Ar-H); 7.77 (d, 2H, Ar-H); 7.79 (d, 4H, Ar-H).

Anal. Calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.23; H, 5.09; N, 3.56. Found: C, 70.14; H, 5.12; N, 3.42.

General Procedure for the Synthesis of γ-Lactams **6a-d**.

Raney nickel (30 eq.) in water/methanol (1:1) was refluxed for 30 min and a mixture of isoxazolidine **3a-d** (1.0 mmol) and formic acid (70 eq.) was added in 5 ml of water/methanol (1:1). After refluxing for 4.0 h, the solution was filtered, diluted with water, neutralized with 10% sodium bicarbonate, washed with brine solution, and finally extracted with dichloromethane. The organic layer was dried, and evaporation to give crude product **6a-d**. Pure products **6a-d** was obtained in 60-73% yield after passing through silica gel column (hexane and ethyl acetate are 8:2).

5-(1,1'-Biphenyl-4-yl)-3-hydroxy-1-phenylpyrrolidin-2-one (**6a**).

This compound was obtained from **3a** according to the general procedure and was crystallized with *n*-hexane. mp: 132-133 °C; ir (Nujol): 1690 cm^{-1}:3220 cm^{-1}; ^1H nmr: (deuteriochloroform): δ 3.38 (dd, 2H, 4-CH_2); 4.42 (t, 1H, CH-N); 4.72 (t, 1H, CH-CO); 5.18 (s, 1H, OH); 7.16 (m, 5H, Ar-H); 7.43 (d, 2H, Ar-H); 7.54 (t, 1H, Ar-H); 7.64 (t, 2H, Ar-H); 7.74 (d, 4H, Ar-H).

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.24; H, 5.77; N, 4.25. Found: C, 80.04; H, 5.25; N, 4.05.

5-(1,1'-Biphenyl-4-yl)-3-hydroxy-1-(4-methyl)phenylpyrrolidin-2-one (**6b**).

This compound was obtained from **3b** according to the general procedure and was crystallized with *n*-hexane. mp: 110-113 °C; ir (Nujol): 1680 cm^{-1}:3200 cm^{-1} ; ^1H nmr: (deuteriochloroform): δ 2.31 (s, 3H, CH_3 -Ph); 3.35-3.51 (dd, 2H, 4-CH); 4.43 (t, 1H, CH-NR); 4.73 (t, 1H, CH-CO); 5.11 (s,1H, OH); 7.21 (d, 2H, Ar-H); 7.39 (d, 2H, Ar-H); 7.42 (d, 2H, Ar-H); 7.52 (t, 1H, Ar-H); 7.62 (t, 2H, Ar-H); 7.74 (d, 4H, Ar-H).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.47; H, 6.12; N, 4.08. Found: C, 80.24; 6.04; N, 4.02.

5-(1,1'-Biphenyl-4-yl)-3-hydroxy-1-(4-methoxy)phenylpyrrolidin-2-one (**6c**).

This compound was obtained from **3c** according to the general procedure and was recrystallized with benzene. mp: 116-119°C; ir (Nujol): 1692 cm^{-1}:3223 cm^{-1}; ^1H nmr: (deuteriochloroform): δ 2.36-3.52 (dd, 2H, 4-CH_2); 3.78 (s, 3H, CH-CO); 4.44 (t, 1H, CH-N); 4.72 (t, 1H, CH-CO); 5.09 (s, 1H, OH); 7.23 (d, 2H, Ar-H); 7.41 (d, 2H, Ar-H); 7.43 (d, 2H, Ar-H); 7.52 (t, 1H, Ar-H); 7.62 (t, 2H, Ar-H); 7.72 (d, 4H, Ar-H).

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.88; H, 5.85; N, 3.90. Found: C, 76.54; H, 5.68; N, 3.67.

5-(1,1'-Biphenyl-4-yl)-3-hydroxy-1-(4-chloro)phenylpyrrolidin-2-one (**6d**).

This compound was obtained from **3d** according to the general procedure and was recrystallized with benzene. mp: 120-125 °C; ir (Nujol): 1685 cm^{-1}:3230 cm^{-1}; ^1H nmr: (deuteriochloroform): δ 3.38-3.54 (dd, 2H, 4-CH_2); 4.45 (t, 1H, CH-N); 4.74 (t, 1H, CH-CO); 5.21 (s,1H, OH); 7.28 (d, 2H, Ar-H); 7.43 (d, 2H, Ar-H); 7.48 (d, 2H, Ar-H); 7.53 (t, 1H, Ar-H); 7.62 (t, 2H, Ar-H); 7.78 (d, 4H, Ar-H).

Anal. Calcd. for $C_{22}H_{18}NClO_2$: C, 72.63; H, 4.95; N, 3.85. Found: C, 72.24; H, 4.80; N, 3.72.

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