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Mild, efficient and diastereoselective one-pot synthesis of substituted oxazolidine under neat conditions

Sachinta Mahato and Adinath Majee*

Department of Chemistry, Visva-Bharati (A Central University), Santiniketan-731 235, West Bengal, India

E-mail: adinath.majee@visva-bharati.ac.in

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A diastereoselective synthesis of substituted oxazolidine systems by one-pot reaction of aromatic aldehydes with L-proline followed by catalyst-free, solvent-free, 1,3-dipolar cycloaddition reactions via non-stabilized azomethine intermediate. The reaction of aldehydes and amino acids produces the azomethine intermediate. NMR spectroscopy as well as single-crystal X-ray crystallographic analysis data have recognized the structures and stereochemistry of formation of the cycloadducts product. The advantages are the clean reaction, commercially available starting materials, metal and solvent-free conditions.

Keywords: One pot, solvent-free, without workup, room temperature, short time.

Introduction

The concept of a chemical reaction without any solvent is one of the most important tools to attain sustainable development in the chemical environment. It has been observed that sometimes solvent-free reactions take place more efficiently and more selectively than conventional reaction. The solvent and catalyst free reaction known as neat reaction is carried out by the reactants only to get the desired product[1,2]. In our recent review[3], we have classified these as Type I where there is no solvent as well as no catalysts[4] and Type II where there is no solvent but there is catalyst[5]. In this work we intend to highlight the real cases where the concept has been proved by real investigation of some important transformation in organic synthesis.

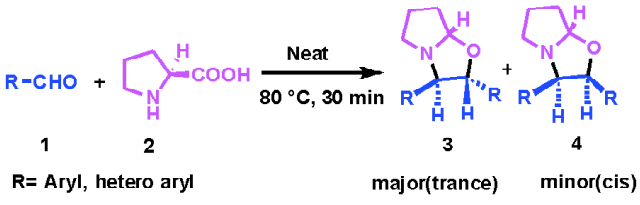
We have investigated the synthesis of oxazolidine for this purpose.

Synthesis of substituted oxazolidine is an important transformation in organic synthesis. One-pot multicomponent reactions using aldehydes and α-amino acids like L-proline have been reported to synthesise the substituted oxazolidine moiety[6]. It acts as central active site in different natural products[1,2,7], catalysts in various reactions[8], and several applications as plasticizers, biocides and pesticides[9–12].

In literature few[1] reports are there to prepare oxazolidine derivatives by different groups. Most of these protocols are based on the reaction of L-proline with aldehydes using base catalyst under microwave irradiation. Different solvents such as DMSO[13], dry DMF[14] and also using Lewis acid[15], metal catalyst like cerium(IV) oxide (CeO_2)[16] etc. are used in the reactions. Reaction of aromatic aldehydes with pyrrolidine and under microwave irradiation also reported in the last decade[17]. But all the above methods have some disadvantages. Herein, we report a catalyst and solvent-free condition at 80°C to synthesize oxazolidine derivatives by the reaction of aryl aldehydes and L-proline (Scheme 1).

Experimental

General information: To determine the melting points glass disk with an electric hot plate has been used. Sample for ^1H NMR(400 MHz) has been prepared usnig $CDCl_3$ solution as



Scheme 1. Synthesis of oxazole derivatives.

well as to record ^{13}C NMR (100 MHz) spectra. Chemical shifts are mentioned in parts per million (δ) and the signals were designated as s for singlet, d for doublet, t for triplet, m for multiplet, dd for double doublet. The corresponding coupling constants (*J*) were expressed in Hz. All the chemicals has been purified in proper process before the reaction.

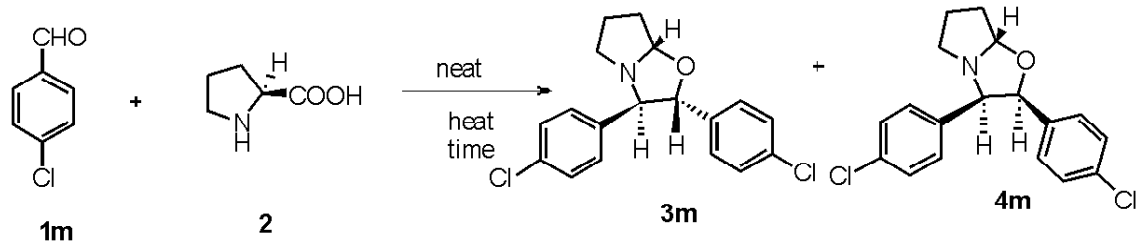
Chemicals have been purchased from standard company like Sigma-Aldrich, Merck, Fluka, Spectrochem, SRI etc. For moisture-sensitive reactants we have used oven-dried glassware.

*General procedure to synthesize 2,3-diphenylhexahydropyrrolo[2,1-b]oxazole (**3** and **4**):* A mixture of benzaldehyde (**1**, 1.5 equiv.) and L-proline (**2**, 1.1 equiv.) was taken in a reaction tube and stirred at 80°C temperature without using any solvent for 30 min. After the completion the crude product (without workup) of the reaction (monitor by TLC), was purified by column chromatography technique using silica gel as stationary phase and petroleum ether/ethyl acetate (4% to 5%) as eluent.

Results and discussion

The reaction of 4-Cl benzaldehyde with L-proline was considered as model reaction to optimize the conditions (Table 1). Initially, the reaction was carried out by taking 4-Cl benzaldehyde (**1m**, 1 equiv.) and L-proline (**2**, 1 equiv.) at 80°C temperature without using any solvent (Table 1, entry 1). The reaction occurred well using this neat conditions with isolated in 65% yield of the desired product **3m** and 5% of **4m** within 30 min. From this initial result, we are inspired and we varying the different ratio of aldehyde and proline. We used 4-Cl benzaldehyde (**1m**, 1.5 equiv.) and L-proline (**2**, 1 equiv.) at 80°C temperature without using any solvent (Table 1, entry 2), we obtained 77% of **3m** product with 7% of **4m** product. Next, we increased the amount of L-proline from 1 to 1.1 (equiv.) interestingly we got the best result with 85% of **3m** product with 10% of **4m** product (Table 1, entry 3). On increasing the amount of 4-Cl benzaldehyde (**1m**) and L-proline (**2**) (Table 1, entry 4) the product was not significantly increased. But the yield was decreased under lower temperature at 60°C (Table 1, entry 7) and the yield of the reaction did not improve significantly at a higher temperature at 100°C (Table 1, entry 8). Interestingly the time variation in the reaction has no influence as mentioned in Table 1, entries 5 and 6. From these above reactions conditions we

Table 1. Optimization of the reaction conditions[a]



Entry	Aldehyde (**1m**, equiv.)	L-Proline (**2**, equiv.)	Temp. (°C)	Time (min)	Conversion (%)	Yield[b] of **3m** (%)	Yield of **4m** (%)
1	1	1	80	30	70	65	5
2	1.5	1	80	30	84	77	7
3	**1.5**	**1.1**	**80**	**30**	**95**	**85**	**10**[b]
4	2	1.5	80	30	96	85	11
5	1.5	1.1	80	20	62	60	trace
6	1.5	1.1	80	60	96	85	11[b]
7	1.5	1.1	60	30	48	46	trace
8	1.5	1.1	100	30	96	86	10[b]

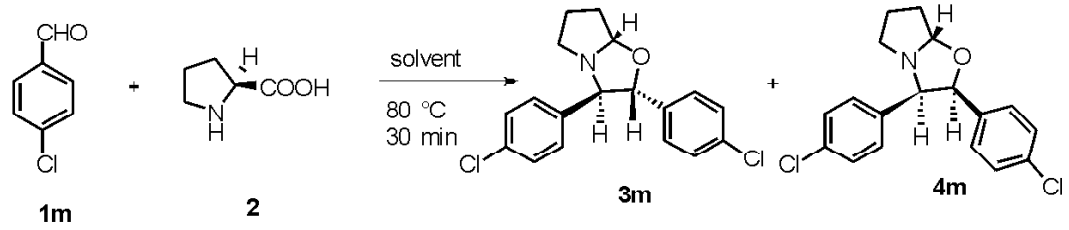
[a]*Reaction conditions:* All reactions are carried out in 0.5 mmol scale, **1m** (1.5 equiv.), **2** (1.1 equiv.) at 80°C temperature for 30 min under neat conditions. [b]Isolated yield.

observed that 1.5 equiv. of aldehyde and 1.1 equiv. of the L-proline gave the best result (Table 1, entry 3). The reaction proceed in neat conditions very well, but we have examined the influence of few common solvents to examine the role of solvents (Table 2). Solvent like DMSO (polar non-protic) gave very small conversion of this reaction (Table 2, entry 3). An amazingly nonpolar non-protic solvent like xylene, DCB the reaction did not proceed significantly (Table 2, entries 5 and 6) and in case of toluene showed small conversion (Table 2, entry 7). In polar non-protic solvents like DMF and 1,2-DCE the overall desired product was observed in 40–60% yields (Table 2, entries 2 and 4). Whereas in case of CH_3CN the desired product was obtained in 62% of 3 h along with 14% of 4 h respectively (Table 2, entry 1) temperature for 30 min (Table 2, entry 8).

It has been observed that under neat conditions at 80°C temperature for 30 min maximum yield was obtained (Table 2, entry 8).

Then substrates scope using this optimising reaction conditions have been examined (Tables 3 and 4). A variety of 2,3-diphenylhexahydropyrrolo[2,1-*b*]oxazole derivatives have been powerfully reacted with L-proline to give the corresponding products. Phenyl moiety of aldehyde substituted by the different electron-donating groups such as methyl (**3b**, **3c**), methoxy (**3d, 3e**) at different positions afforded the desired products in good to excellent yields with the exclusively *trans* product. Even simple phenyl moiety also gave the good yield (**3a**). Interestingly, 2-substituted electron-withdrawing groups like halogen (**3f**, **3g**), trifluoromethyl (**3h**) only produced the *trans*-oxazole derivatives in good yields. Then our attention was turned to the use of heterocyclic moieties like 2-thiophene carboxaldehyde reacted well under the optimized reaction conditions (**3i**). Piperonal with acid-sensitive group offered good amount of desired product (**3j**) keeping the other groups unaffected. This proofs the mildness of the present optimized reaction conditions and gave selectively *trans* product. 1-Napthyl benzaldehyde (**3k**) also produce the desired product with good yield. Next, we are pleased to report that in case of maximum electron-withdrawing substituent like halogens (F, Cl and Br) (**3l**-**3o**/**4l**-**4o**), nitro (**3p**-**3r**/**4p**-**4r**), -SCH_3 (**3s**/**4s**) gave the mixture of oxazole derivative efficiently with good to excellent yield. 2-Naphthyl substituent also gave good result (Table 4, **3u**/**4u**). Similarly, methyl carboxylate group (-CO_2Me, **3t**/**4t**) successfully produced both oxazole derivatives with good yield. Yet, aliphatic aldehydes and L-proline did not respond to produce the desired product under the

Table 2. Screening of the solvent effects[a]

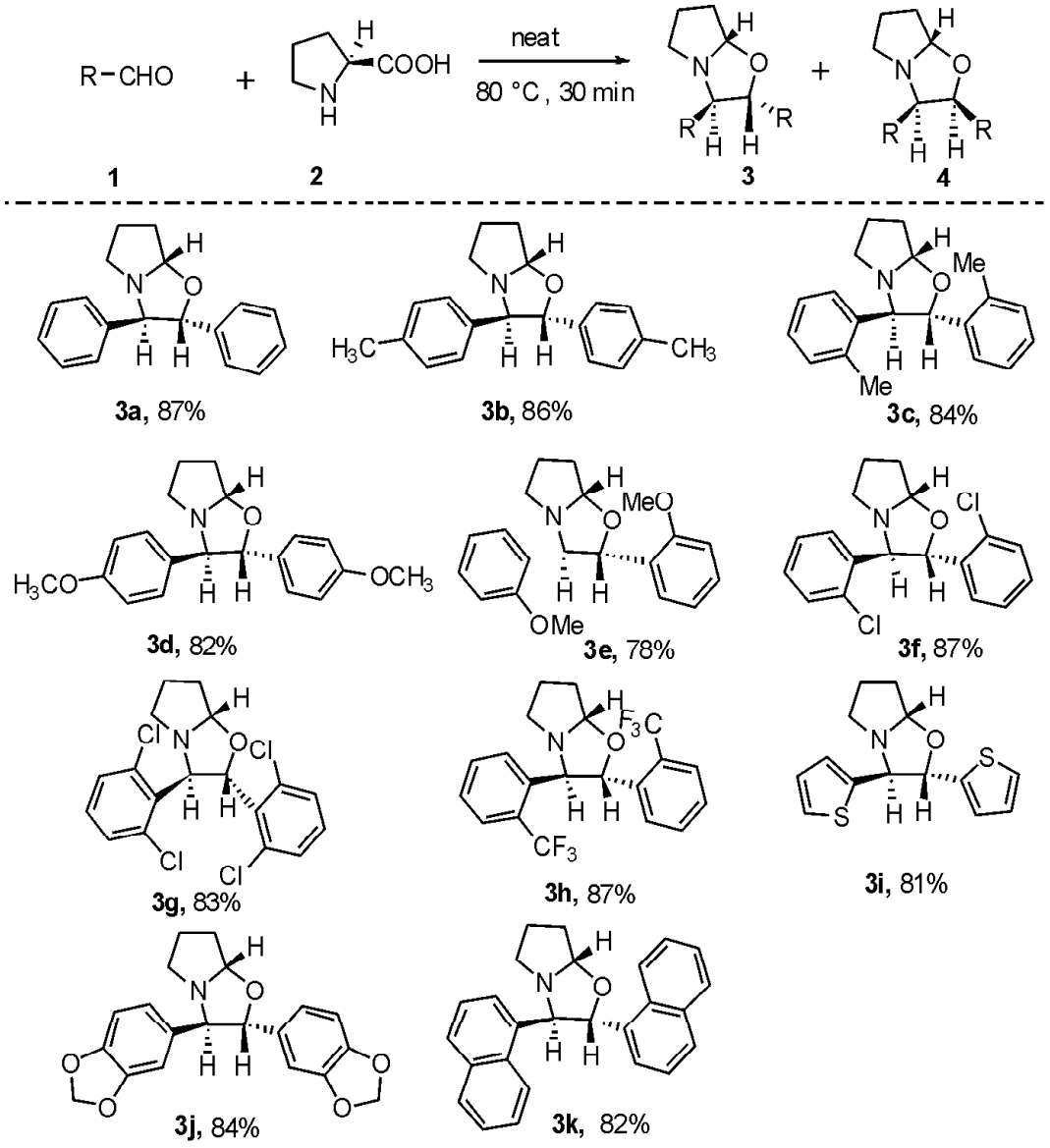


1m **2** **3m** **4m**

Entry	Aldehyde (**1m**)	L-Proline (**2**)	Solvent (mL)	Conversion(%)	Yield [b] of **3m** (%)	Yield of **4m** (%)
1	**1**m	2	CH_3CN	76	62	14
2	**1**m	2	DMF	72	60	12
3	**1**m	2	DMSO	48	38	10
4	**1**m	2	DCE	46	40	<10
5	**1**m	2	DCB	7	trace	Trace
6	**1**m	2	Xylene	4	trace	Trace
7	1m	2	Toluene	27	25	Trace
8	**1m**	**2**	**neat**	**95**	**85**	**10**

[a]*Reaction conditions:* All reactions are carried out in 0.5 mmol scale **1m** (1.5 equiv.), **2** (1.1 equiv.) at 80°C temperature in different solvents (2 mL).
[b]Isolated yields.

Table 3. Synthesis of various 2,3-diphenylhexahydropyrrolo[2,1-*b*]oxazole derivatives[a,b]



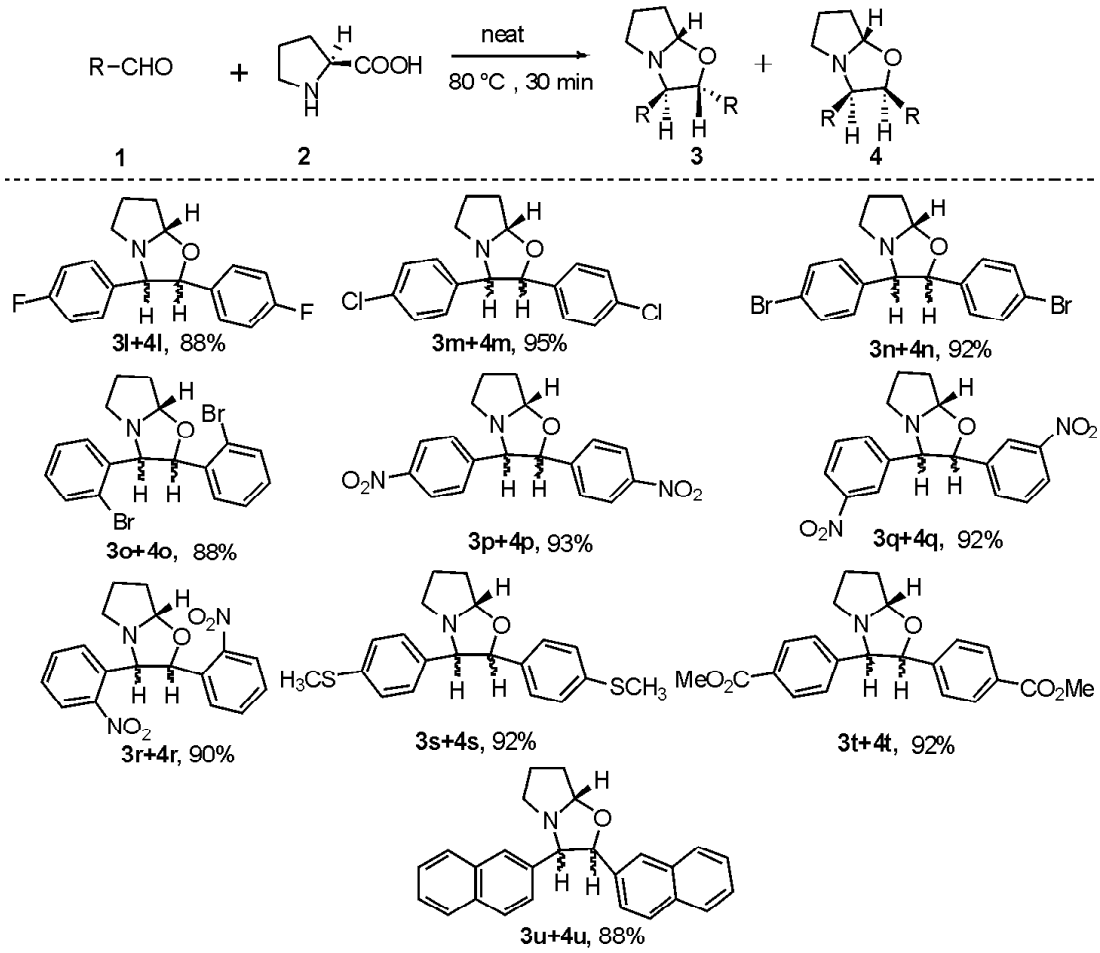
[a]*Reaction conditions:* All reactions are carried out in 0.5 mmol scale, **1** (1.5 equiv.), **2** (1.1 equiv.) at 80°C temperature under the neat condition for 30 min. [b]All are isolated yields.

present reaction conditions.

Based on our reactions and literature[6,14,17], we have proposed a probable mechanism for this reaction (Scheme 2). Initially, the formation of the iminium ion intermediate (**A**) takes place by the reaction between L-proline and aldehyde and at the same time carboxylate ion also form. After that, **A** transformed into nonstabilized intermediate (**X** and **Y**) followed by decarboxylation of **B**. Next, the 1,3-dipolar cycloaddition reaction occurs between excess aldehyde and the intermediate **X** afforded the corresponding oxazole derivatives (**3** and **4**).

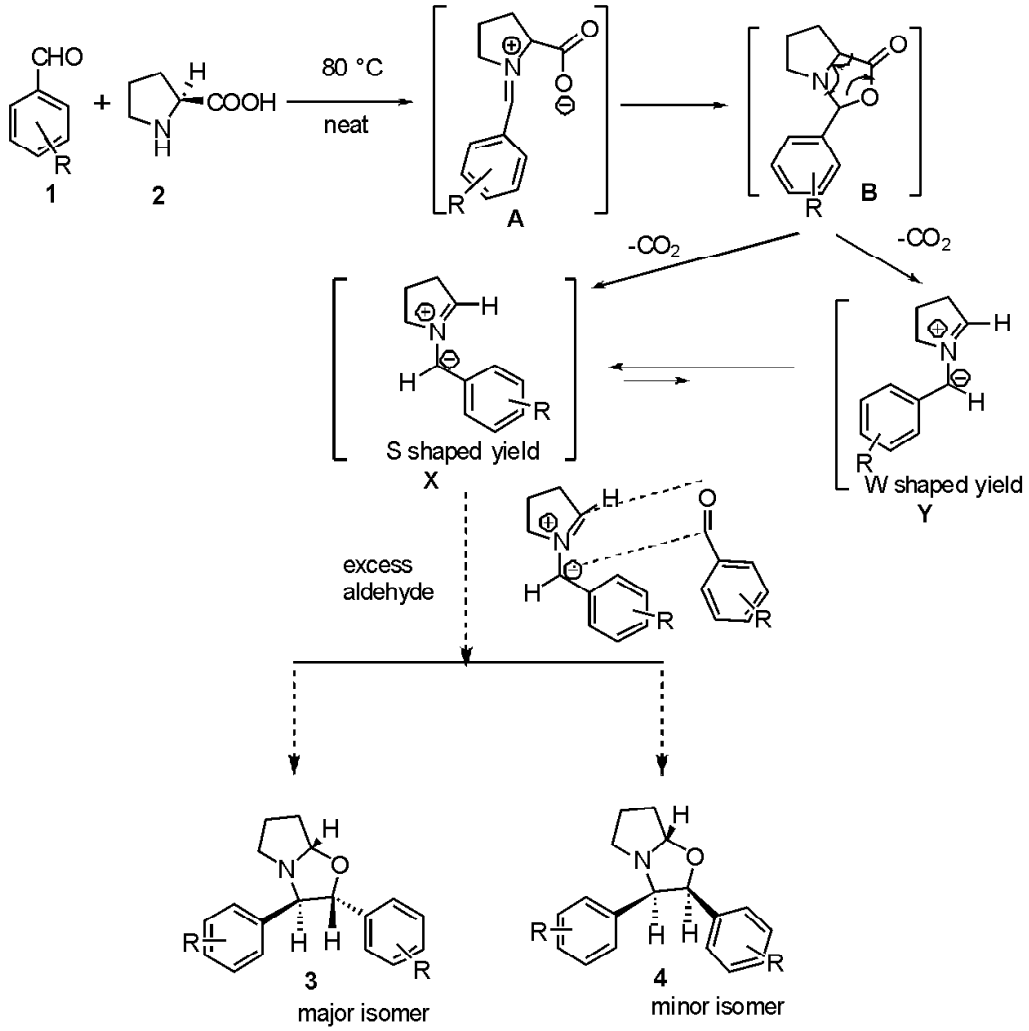
So, it was observed that two oxazole derivatives

Table 4. Synthesis of various 2,3-diphenylhexahydropyrrolo[2,1-*b*]oxazole derivatives[a,b]



[a]*Reaction conditions:* All reaction are carried out in 0.5 mmol scale, **1** (1.5 equiv.), **2** (1.1 equiv.) at 80°C temperature under the neat condition for 30 min. [b]All are isolated yields.

(diastereomeric in nature)[6,14] were formed from our experimental results as well as mechanistic pathway. The most likely due to minimum steric repulsion, cyclo product (**3m**) was the major isomer and **4m** was the minor one and due to the difference in coupling constant between H^b and H^c. For coupling constant J = 8.0 Hz of **3m** (between H^b and H^c) and J = 5.6 Hz of **4m** (between H^b and H^c) i.e. **3m** and **4m** are *trans* and *cis* product (Fig. 1). Again, also coupling constant J = 8.0 Hz of **3p** (between H^b and H^c) and J = 6.0 Hz of **4p** (between H^b and H^c) which make easy to differentiate between *trans* and *cis* isomers. Alternatively, from single-crystal X-ray crystallographic data analysis of compound **3p** (as shown Fig. 2), it could be concluded that H^b and H^c protons of compound **3p** were oriented in *trans* fashion. So, based on literature and above result it is clear that the value of coupling constant the two protons H^b and H^c shows *trans* and *cis* fashion. Hence from the above observation, it was liable to guess the type of stereochemistry of oxazole de-



Scheme 2. Plausible reaction mechanism for the synthesis of oxazole derivatives.

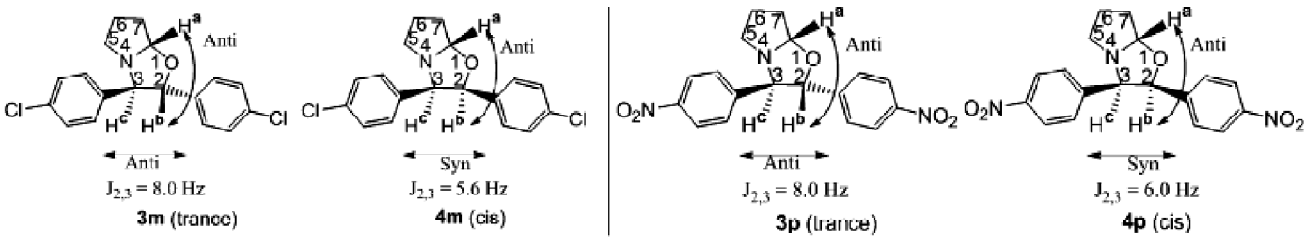


Fig. 1. Confirmation of the relative stereochemistry of the compound **3m**/**4m** and **3p**/**4p**.

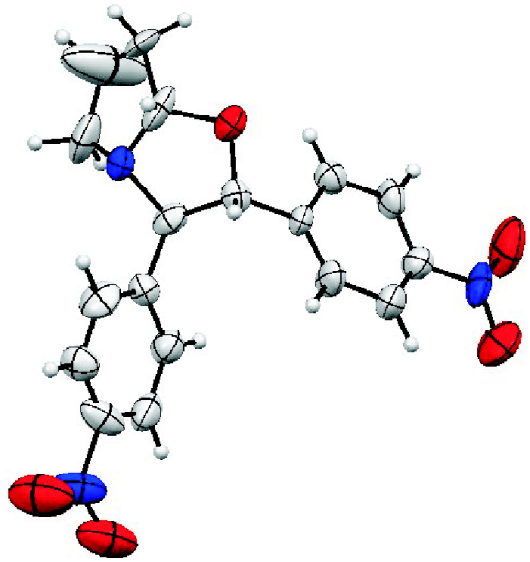


Fig. 2. The single crystal XRD structure of compound **3p**.

rivatives and *trans* cycloadduct product is major and *cis* is a minor one.

Conclusions

In conclusion, we have reported a suitable approach to synthesize various 2,3-diphenylhexahydropyrrolo[2,1-*b*]oxazole derivatives from aldehydes and L-proline under the neat condition at 80°C. A sequence of oxazole derivatives has been synthesized by employing the optimized reaction condition. Aryl, as well as heteroaryl substitute with a range of functionalities, formed the consequent cycloadduct products with high yields. In most of the cases, the diastereoselectivity was tolerable without using any chiral auxiliary or chiral catalyst in our present methodology (Tables 3 and 4). During optimization, it was observed that no external solvent was required to fulfil the reaction conditions. The remarkable advantages of our methodology are clean reaction, mild conditions, ease of product separation/purification, readily available reactants, wide substrates scope, metal catalyst-free, solvent-free and environmentally friendly reaction conditions.

Acknowledgements

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Supporting Information

^{1}H and ^{13}C NMR data of all the synthesized compound are given in supporting information file. Crystallographic data for the structure of **3p** has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 1974278.

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