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Synthesis of α- cyanostyrylbenzimidazoles under solvent-free conditions using L-proline as catalyst: A green approach

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ABSTRACT

*A simple and green methodology for the Knoevenagal condensation of 2-(1H-benzimidazol-2-yl)acetonitrile **3** with benzaldehydes **4(a-h)** yielding 2-(α-cyanostyryl)benzimidazole **5(a-h)** has been developed under solvent-free (physical grinding) conditions and also under solution phase using ethanol as solvent with L-proline as a catalyst. Compounds **5(a-h)** were alternatively prepared by the Knoevenagal condensation of ethyl cyanoacetate **2** with **4(a-h)** by simple physical grinding using L-proline as catalyst, yielding ethyl 2-cyano-3-phenylacrylate **6(a-h)**, and subsequent treatment with o-phenylenediamine **1** by simple heating. N-Methylation of **5a** was done under physical grinding conditions using tetrabutylammonium bromide (TBAB) as surface catalyst and K_2CO_3 as base yielding 2-(1-methyl-1H-benzimidazol-2-yl)-3-phenylacrylonitrile **8a** in good yield. **8a** was alternatively prepared by the Knoevenegal condensation of (1-methyl-1H-benzimidazol-2-yl) acetonitrile **7** with **4a** under solid phase synthesis using L-proline as catalyst. **7** was prepared by the methylation of **3** under physical grinding. 3 in turn was obtained by the condensation of **1** and **2** under simple heating conditions. The entire sequence of reactions was done under green conditions.*

Keywords: Benzimidazoleacetonitriles, aromatic aldehydes, L-Proline, solvent-free conditions.

INTRODUCTION

Benzimidazole derivatives are an important class of compounds, many of which have been reported to posses important biological activities [1] such as anti-bacterial [2], anti-fungal [3], anti-parkinsons [4], anti-cancerous [5], anti-viral [6] and so on. There is thus a considerable interest in synthesis of differently substitutedbenzimidazoles, more so using green conditions.

Present investigation describes condensation of a benzimidazole derivative having an active methylene group with benzaldehydes using Knoevenagal condensation. The latter reactions are useful for carrying out new carbon-carbon bond formation reactions. These reactions are known to be catalyzed by bases [7] such as amines, ammonia, piperidine, sodium hydroxide, sodium alkoxides[8] etc. and also by, Lewis acids[9], surfactants[10], zeolites[11], mesoporous molecular sieves[12] etc. In the present work, the use of L-proline as catalyst has been described. The choice for L-proline as catalyst was due to its use in many reactions such as Mannich reaction [13], Michael reaction [14], Diels-Alder reaction [15], aldol Condensation [16] and Knoevenagal Condensation [17].

It was reported earlier from these laboratories [18] that the active methylene group in 2-(1H-benzimidazol-2-yl) acetonitrile **3** could be condensed with substituted benzaldehydes **4** yielding **5** using piperidine as base. Hranjec *et.al*. reported [19] the condensation of **3** with 4-*N,N*-dimethylamino-benzaldehyde using piperidine in absolute ethanol under refluxing conditions for 4 hrs. Mugnaini *et.al.* reported [20] the condensation of **3** with substituted furfuraldehydes using piperidine as base in ethanol under refluxing conditions for several hrs. Hranjec *et.al*. once again reported[21] the condensation of **3** with substituted benzaldehydes using piperidine in absolute ethanol for 2-4 hrs under refluxing conditions. Refaat *et.al.* carried out the condensation[22] of **3** with *p*-fluro-benzaldehyde using KOH as base in *N,N*-dimethylformamide in refluxing conditions for 2-3 hrs.

It was obvious from the above data, that the conditions were carried out using prolonged times, refluxing conditions and use of either non-green catalysts or non-green solvents. We have now carried out these reactions using L-proline as catalyst under completely green conditions.

MATERIALS AND METHODS

Experimental Section

Melting points were uncorrected and are determined in open capillary tubes in sulphuric aicd bath. TLC analysis was performed on silica gel-G; visualization was done using UV-light. IR spectrum was recorded using Perkin-Elmer 1000 instrument in KBr phase method. Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}+1$ or $M^{+\cdot}-1$ values and ^{1}H NMR on VARIAN 400 MHz instrument.

i) General procedure for the styrylation of 3 &7(a-e) under solid phase condition:

A mixture of **3** or **7(a-e)** (10 mmol), L-proline (15 mol %, 0.17 gm) and substituted benzaldehydes (10 mmol) was taken in a mortar and grounded with pestle. The progress of the reaction was monitored by TLC. After completion of the reaction 20 ml of distilled water was added to the reaction mixture, separated solid was filtered out and washed with cold water (2x10 mL) and dried to obtain crude product. The latter were recrystallized using ethanol as solvent to obtain pure **5(a-h)** or **8(a-e)**.

ii) General procedure for the styrylation of 3 &7(a-e) under solution phase conditions:

To a stirred solution of substituted benzaldehydes (10 mmol) and L-proline (15 mol %, 0.17 gm) in ethanol (10 mL), **3** or **7(a-e)** (10 mmol) was added at RT Completion of the reaction was monitored using TLC analysis. Separated solid was filtered, washed with cold ethanol (2x10 mL) and dried to obtain crude. The latter were recrystallized using ethanol as solvent to obtain pure **5(a-h)** or **8(a-e)**.

iii) General procedure for N-Alkylation of 3 and 5(a-e) under solid phase conditions:

To a mixture of tetrabutylammonium bromide (PTC, 0.2 gm), K_2CO_3 (1.4 gm, 10 mM), **3** or **7(a-e)** (10mM) and dimethylsulphate (1.2 mL, 10 mM) was taken in a mortar and grounded with pestle. The progress of the reaction was monitored by TLC. After completion of the reaction, 20 ml of distilled water was added to the reaction mixture, separated solid was filtered out and washed with cold water (2x10mL) to obtain crude **7(a-e)** or **8(a-e)**.. Crude product was then recrystallized using ethanol as solvent.

iv) General procedure for N-Alkylations of 3 and 5(a-e) under solution phase conditions:

To a mixture of K_2CO_3 (1.4 gm, 10 mM) and **3** or **5(a-e)** (10mM) in ethanol (10 mL), dimethylsulphate (1.2 mL, 10 mM) was added under stirring at RT. The reaction progress was monitored by TLC, after the completion of reaction, the separated solid was filtered and the insoluble material washed with cold ethanol (2x5 mL). The ethanol filtrate was evaporated to get crude **7(a-e)** or **8(a-e)**. The obtained crude was recrystallized using ethanol as solvent.

v) General procedure for the preparation of 3 and 5(a-h) under thermal conditions:

Mixture of **1** and **2** or **6(a-h)** were heated on oil-bath at 110° C, where the clear solution appeared. Heating continued till the disappearance of starting materials in TLC. After the completion of reaction, 10 mL of ethanol was added to reaction mass. Distill off the ethanol to obtain crude product, which in turn was washed with cold water. Crude product thus obtained was recrystallized using ethanol as solvent.

RESULTS AND DISCUSSION

o-Phenylenediamine **1** was condensed with ethyl cyanoacetate **2** using literature method[22] to obtain 2-(1H-benzimidazol-2-yl)acetonitrile **3**. Condensation of **3** with benzaldehyde **4a** was done, in the presence of L-proline as catalyst, under solvent-free conditions by simple physical grinding of reactants at RT using a mortar and pestle for 3-5 minutes. Aqueous workup resulted in the formation of 2-(α-cyanostyryl)benzimidazole **5a** in 95% yields. When the same reaction was carried out under solution phase conditions using ethanol as solvent and L-proline as catalyst at RT for 15 mins, **5**a was obtained in 80% yield. When the reaction of **3** with **4a** was attempted under catalyst free conditions *i.e*. without the use of L-proline, whether in solid phase or in solution phase, it led to the recovery of starting materials even after treating the reactants for 4-5 hrs.

The effect of solvent on the reaction was checked by carrying out the same reaction in other green solvents as well as in non-green solvents. Green solvents used were water, ethanol, acetic acid, glycerol, methyl lactate and PEG-600 Among all of these solvents, ethanol proved to be the best as far as yield & purity of the product was concerned (**Table-I**).

Table I: Reaction of 3 with benzaldehyde 4a in various green solvents at RT.

Entry	Solvent	Time (Mins)	Yield (%)
1	Water	25	75
2	Ethanol	15	84
3	Acetic acid	25	70
4	Glycerol	30	70
5	PEG-600	35	80
6	Ethyl Lactate	25	60

The same set of reactions was also carried out using various non green solvents, like DMF, acetonitrile, 1, 4-dioxane, benzene and methylene-dichloride (MDC), methyl ethyl ketone respectively. It has been observed that, though the above solvents were efficient in carrying out the reaction, results were not as good as green solvents (**Table-II**). Among the both non green and green solvents used, ethanol proved to be the best as far as yield and purity of the compounds concerned.

Table II: Reaction of 3 with benzaldehyde 4a in various Non-green solvents at RT.

Entry	Solvent	Time (Mins)	Yield (%)
1	DMF	15	70
2	Acetonitrile	20	75
3	1,4-dioxane	30	60
4	Benzene	60	50
5	Methylene dichloride	85	30
6	Ethyl methyl ketone	80	55

The reaction of **3** with **4a** has also been studied using other amino acid catalysts, other than L-Proline. Amino acids like glycine, L-alanine, L-leucine, L-serine, L-tryptophan and L-phenylalanine were used as catalysts in the reaction. Among the catalysts used L-tryptophan gave moderate to good yields compared to other amino acids used. Results are summarized in Table **III**.

Table-III: Reaction of 4a with 3 using different L-Amino acids, as catalyst at RT.

Entry	Catalyst (15 mol %)	Solution Phase in ethanol		Solid Phase	
		Time (min)	Yields[a] (%)	Time (min)	Yields[a] (%)
1	Glycine	25	55	15	60
2	L-alanine	30	45	10	59
3	L-phenylalanine	15	50	20	58
4	L-leucine	25	45	15	55
5	L-serine	35	40	10	60
6	L-tryptophan	25	50	10	72

[a] *Refers to* ***5a*** *Isolated crude yields.*

The optimum concentration of the catalyst (Lproline) required in the above reaction was also studied by changing the concentration of the catalysts from 10, 15, 20, 25, 30 and 40 mole percentages. Maximum yields were obtained

with the concentration being 15 Mol%. No further change in the yields of the products was observed even increasing the concentration of the catalyst from 20-40 mol%. These results were shown in **Table-IV**.

Table-IV: Mole percentage calculated data for L-Proline.

Entry	Catalyst (Mol %)	Solution Phase in ethanol		Solid Phase	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	L-proline (10%)	8	83	5	83
2	**L-proline (15%)**	**10**	**90**	**3**	**94**
3	L-proline (20%)	9	89	3	94
4	L-proline (25%)	10	86	3	92
5	L-proline (30%)	10	85	4	94
6	L-proline (40%)	10	85	5	92

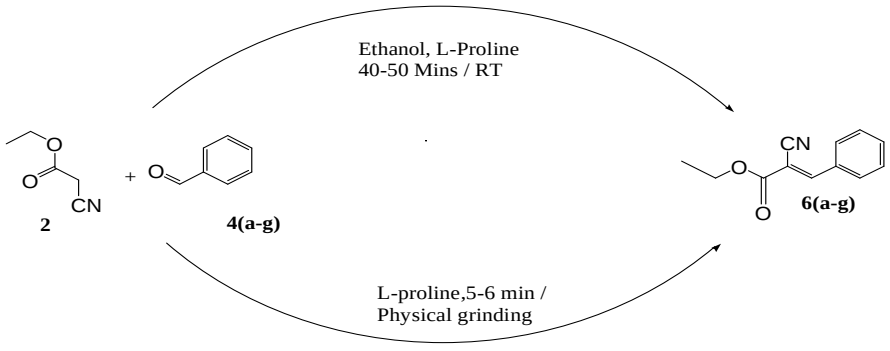
Using all the optimised conditions described above, reaction of 3 with other aromatic aldehydes **(4b-g)** was carried out and the products 7(b-g) were obtained. The results are summarized in **Table-V.**

Table-V: Synthesis of benzimidazole derivatives using L-proline (15 mol %) as catalyst.

Substrate (3)	Ar-CHO (4)	Product	M.P (^{0}C)	Solution Phase(EtOH)		Solid Phase	
				Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
3	-C_6H_5 **4a**	5a	215	12	84	4	94
3	-$C_6H_4CH_3$-*p* **4b**	5b	246	15	85	5	90
3	-$C_6H_4OCH_3$-*p* **4c**	5c	>250	10	80	5	92
3	-$C_6H_4NHCOCH_3$-*p*	5d	>250	12	85	5	90
3	-$C_6H_4N(CH_3)_2$-*p* **4d**	5e	>250	15	78	12	85
3	-$C_6H_3OCH_3$-*m*-(OCH_3) **4e**	5f	181	15	75	6	92
3	-C_6H_4Cl-*p* **4f**	5g	>250	15	85	10	90
3	-C_6H_4F-*p* **4g**	5h	>250	15	81	10	91
7	-C_6H_5 **4a**	8a	122	10	85	12	93
7	-$C_6H_4CH_3$-*p* **4b**	8b	111	19	80	15	90
7	-$C_6H_4OCH_3$-*p* **4c**	8c	138	10	75	15	91
7	-$C_6H_4N(CH_3)_2$-*p* **4d**	8d	166	20	80	11	85
7	-$C_6H_3OCH_3$-*m*-(OCH_3) **4e**	8e	158	10	85	9	88

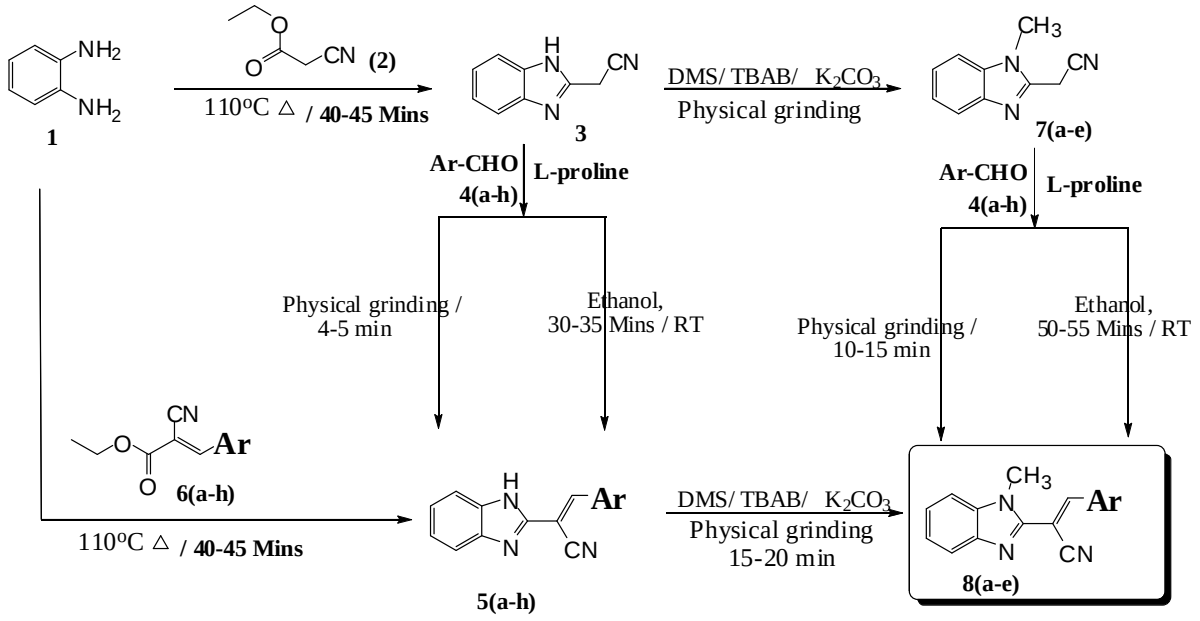
[a]*Isolated yields of final products.*

Alternatively **5a** could also be prepared by the condensation of **1** with ethyl 2-cyano-3-phenylacrylate (**6a)** by direct heating at 110°C in an oil bath for 40-45 mins in 45 % yield. **6a** itself was prepared by the Knovenagal condensation of **2** with **4a** under solid phase conditions by simple physical grinding of the reactants in the presence of L-proline as catalyst in 90% yield. When the reaction of **2** with **4a** was performed in solution phase, using L-proline as catalyst and ethanol as solvent for 40 minutes under stirring conditions at RT gave **6a** was obtained in 70% yield(**Scheme-I)**. The reaction of **2** with **4** was extended to other substituted benzaldehydes **4(b-h)** in solid phase as well as in solution phase to obtain **6(b-h)**.



Scheme-I

Treatment of **5a** with dimethylsulphate (DMS) in the presence of K_2CO_3 as base in ethanol as solvent, at RT for 2-3 hrs gave **(8a)** in 80-85 % yields. Methylation was also done under simple solid phase physical grinding, where K_2CO_3, DMS, **5a** and TBAB as surface catalyst were grounded for 15-20 mins yielded **8a** in 75 % yield. The obtained results were little less than those obtained in solution phase conditions. Compound **7** could be readily prepared by methylation of **3** under physical grinding conditions. All the above reactions are summarized in **Scheme –II**.



Scheme-II

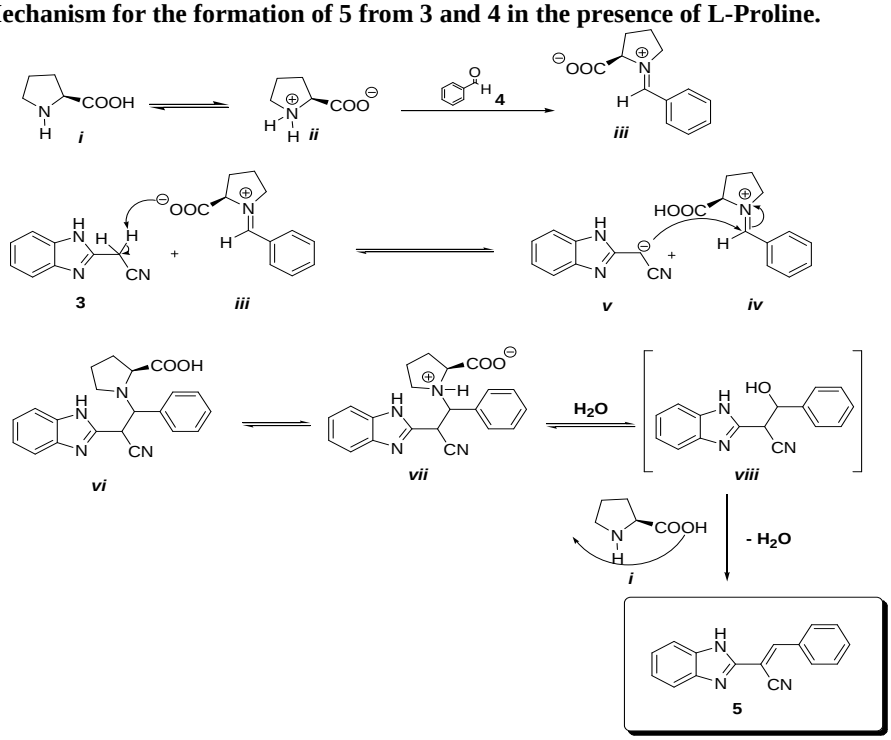
It may be mentioned here that the compounds **5** and **8** respectively have been assigned E-configurations in preference to Z-configuration on the basis of the following considerations: **(i)** The products of condensation between **3** and 4-*N*,*N*-dimethylamino-benzaldehyde were earlier assigned E-configuration on the basis of X-ray crystallographic data. (ii) The products of condensation between **3** & **4** and between **7** & **4** will be presumably having a thermally stable configuration, since in the products **5** & **8** the bulkier groups (heteryl and aryl) have a trans dispensation. This is further supported by the fact that a careful construction of the frame work models of these compounds (**5** and **8** respectively) showed absolutely no non-bonded interactions between bulky aryl & heteryl groups. More over a careful study of the confirmations of these molecules (**5** and **8** respectively) using the molecular modeling software programmes, showed them to be almost free of any steric strains.

Plausible Mechanism for the formation of 5 from 3 and 4:

A plausible mechanism for the formation of **5** from **3** and **4**, when L-Proline is used as catalyst is shown in scheme **IV**. The mechanism is based on the earlier report[23] involving the condensation of indole-3-carboxaldehyde with cyanoacetyl indoles.

The mechanism may plausibly follow the formation of iminium intermediate ***iii,*** which is formed in a reversible reaction when L-Proline in its zwitter ionic form reacts with aromatic aldehyde(**4**). The higher reactivity of iminium ion compared to the carbonyl species could facilitate the reaction by abstracting the proton from the active methylene group of **3** and form a carboxylic acid containing iminium ion ***vi***. The formed iminium ion eventually releases L-proline with the displacement of one water molecule to form continues unsaturated molecule **5**. The released L-Proline once again enters into the reaction and forms a repetitive cyclic path **(Scheme-III)**.

Scheme III: Mechanism for the formation of 5 from 3 and 4 in the presence of L-Proline.



CONCLUSION

In conclusion we have demonstrated a very simple and highly efficient method for the condensation of 2-(1H-benzimidazol-2-yl)acetonitrile and 2-(1methyl-benzimidazol-2-yl) acetonitrile with different aromatic benzaldehydes to give Knoevenagal products in excellent yields. The solvent free system (physical grinding) gave promising results and L-proline appeared to be the best catalyst for this reaction. All the performed reactions were done under complete green conditions.

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