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Multi-component synthesis and recent development on heterocyclic compounds: A research

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Abstract
Heterocyclic compounds have a significant role in our daily lives. These compounds make up the biggest and most diverse organic compound family. Heterocyclic compounds have one or more hetero atoms in their molecular structure. The number of heterocyclic compounds is growing fast as a result of extensive synthetic research and their usefulness in synthetic chemistry. They might be cyclic or acyclic. Primarily, they are utilized as medications, agrochemicals, and veterinary goods. In addition, they are used as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, colouring agents, and anticancer medicines. They are utilized as vehicles in the synthesis of other organic molecules. In this article, we discuss the majority of newly synthesized or extracted biologically active heterocyclic compounds, such as antibiotics like penicillin and cephalosporin and alkaloids like vinblastine, morphine, and reserpine. In this research, we concentrate on multicomponent reactions of several recent synthetic applications of these innovative approaches.

Keywords: Biological activity, medicinal chemistry, heterocyclic compounds, chromenes

Introduction
Heterocyclic compounds are cyclic organic compounds that contain at least one hetero atom. Nitrogen, oxygen, and sulfur are the most frequent heteroatoms, although heterocyclic rings containing additional hetero atoms are also well-known [1-11]. A carbocyclic compound is a ring-shaped carbon-containing organic cyclic compound.
The most frequent heterocycles comprise nitrogen (N), oxygen (O), or sulfur (S) heteroatoms and have five- or six-membered rings (S). Among the simple heterocyclic compounds, pyridine, pyrrole, furan, and thiophene are the most well-known [12-21]. Five carbon atoms and one nitrogen atom make up the ring of a pyridine molecule. Each molecule of pyrrole, furan, and thiophene has a five-membered ring comprised of four carbon atoms and one element of nitrogen, oxygen, or sulfur, respectively. Both pyridine and pyrrole are nitrogen heterocycles; their ring molecules include both nitrogen and carbon atoms.
Modern organic synthesis places a high priority on multicomponent reactions (MCRs) because they allow the coupling of three or more initial components to create an adduct in a single step, resulting in excellent atom economy and bond-forming efficiency. Since MCRs historically regarded heterocycles as either the products (As in the conventional MCRs) or as the substituents of reactive functional groups, the heterocyclic moiety may be included into the final adduct. The third (and most versatile) choice involves using heterocycles directly as reagents in MCRs. By utilizing this modular approach, innovative drug-like scaffolds with heterocyclic motifs might be made, taking advantage of the high heterocyclic reactivity. Additionally, it makes it easier to research the response mechanisms in these systems. In this post, we present a number of research results that demonstrate the effectiveness of this strategy.

Results and Discussion
Heterocyclic compounds comprising nitrogen, oxygen, and sulfur atoms are commonly prevalent in a variety of natural products and physiologically active molecules, functional materials, ligands, and catalysts, and are also utilized in organic synthesis as versatile building blocks. Particularly, several pharmaceuticals and agrochemicals include heterocyclic moieties.

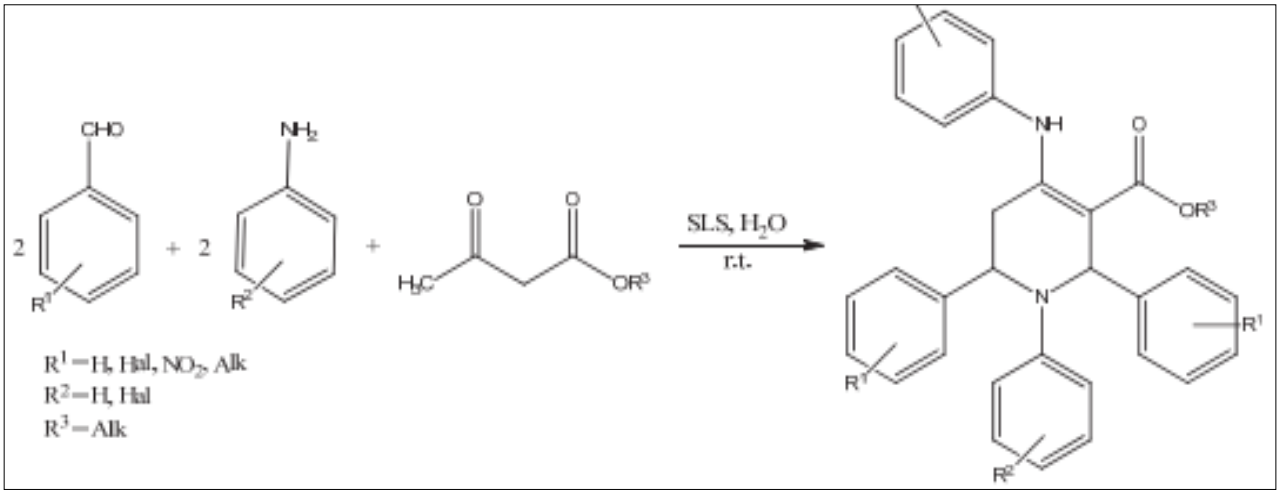
Significant effort has been expended on the development of synthetic techniques for the synthesis of heterocyclic molecules. In the continuing of our research program aimed at the development of novel synthetic techniques for the creation of a variety of heterocyclic compounds under moderate and eco-friendly circumstances, we will continue to focus on the synthesis of new approaches.

One-pot multi-component synthesis of substituted piperidines

Substituted piperidines are widely present in naturally occurring and synthetic drugs. A variety of structural features are exhibited by synthetically prepared piperidines including many significant biological activities. Many methods have been extensively studied for the synthesis of piperidines because of their anti-histamic, anti-HIV, anticancer, antimicrobial, anti-malarial, anti-inflammatory, insecticidal and other biological activities.

Recently, many MCRs have been reported for the syntheses of piperidine derivatives in the presence of L-proline/tetrahydrofuran (THF), indium trichloride (InCl3), bromodimethyl sulfonium bromide (BDMS), tetrabutylammonium tribromide (TBATB), iodine, cerium ammonium nitrate (CAN), ZrOCl2·8H2O, citric acid, calix[n]arenes, tris (Pentafluorophenyl) borane [B(C6F5)3], sulfamic acid and 2,6-pyridinedicarboxylic acid used as catalysts. Some of these methods are having such draw backs as long reaction times, unsatisfactory yields or use of expensive catalysts. All these prompted us to develop a new simple and greener method of the synthesis of piperidines.

In the present communication we have reported a simple and efficient procedure of one-pot multi-component synthesis of highly substituted piperidines by the reaction between aromatic aldehydes, anilines and β-ketoesters in the presence of SLS, used as a catalyst, under mild reaction conditions at room temperature (Scheme 1). SLS is cheap, readily available, versatile, environment friendly and recyclable. The reactions have been carried out in water, what eliminated the use of organic solvents.



Scheme 1: One-pot multi-component synthesis of substituted piperidines

Initially benzaldehyde (2 mmol) was treated with aniline (2 mmol) and ethyl acetoacetate (1 mmol) with water in absence of catalyst. No product was obtained at room temperature after 24 h (Table 1, entry 8). To determine the best experimental conditions, the reaction was carried out in the presence of 0.02 g SLS in water at 100 ºC. The reaction proceeded smoothly to give the corresponding functionalized piperidine in 30% yield after 24 h (Table 1, entry 13). When the same reaction was carried out under solvent-free conditions, the product was obtained 25% yield after 24 h (Table 1, entry 14). The best results were obtained in the presence of 0.02 g SLS in water at room temperature (Table 1, entry 9).

Table 1: Condensation of benzaldehyde, aniline and ethyl acetoacetate in different conditions

Entry	Catalyst	Solvent	Time, h	T, ºC	Yield, %
1	NiCl2	Water	24	50	40
2	ZnO	Ethanol	24	80	No product
3	Fe2O3	Ethanol	24	70	No product
4	CaO	Ethanol	8	80	No product
5	L-Prolin	Ethanol	10	80	40
6	CaO	Ethanol	14	60	No product
7	Al2O3	Ethanol	10	50	No product
8	Without catalyst	Water	24	r.t.	No product
9	SLS	Water	6	r.t.	95
10	Twine-20	Water	10	50	No product
11	Cetrimide	Water	10	r.t.	No product
12	Triton X-100	Water	10	r.t.	No product
13	SLS	Water	24	100	30
14	SLS	Without Solvent	24	r.t.	25

Conditions: benzaldehyde (2 mmol), aniline (2 mmol), ethyl acetoacetate (1 mmol), solvent (10 mL), catalyst (0.02 g)

Several substituted benzaldehydes, anilines, methyl/ethyl acetoacetates (EAA) were examined under the optimized reaction conditions. Benzaldehydes with EWG (electron withdrawing) groups underwent the reaction with anilines efficiently to give the corresponding piperidines in moderate to high yields. Aldehydes possessing the EDG groups e.g. -CH3 were less reactive (Table 2, entry 9).

Table 2: Synthesis of substituted piperidines.

Entry	R1	R2	R3	Product	Time, h	Yield, %	M.p., ºC
1	H	H	Et	4a	6	90	174
2	H	4-Cl	Et	4b	6	85	220
3	2F	H	Et	4c	7	65	128
4	4-Cl	H	Et	4d	6	95	215
5	4-NO2	H	Me	4e	6	80	236
6	3-NO2	H	Et	4f	7	80	247
7	4-F	H	Et	4g	6	80	170
8	H	4-F	Et	4h	7	80	144
9	4-Me	4-Cl	Et	4L	8	75	234
10	4-OH	H	Et	4j	6	90	233

Conditions: aromatic aldehyde (2 mmol) aromatic amine (2 mmol), β-ketoester (1 mmol), SLS (0.02 g), water (10 mL), room temperature

The structures of newly synthesized compounds 4a-4j has been confirmed based on the 1H NMR, C NMR and FT-IR spectroscopic and elemental analysis data.

The temperature seems does not have any significant effect on the products yield. The yields of the products did not also improve when the amount of SLS was increased. The results are presented in Table 3.

Table 3: Effect of SLS loading on the synthesis of piperidine 4a at room temperature

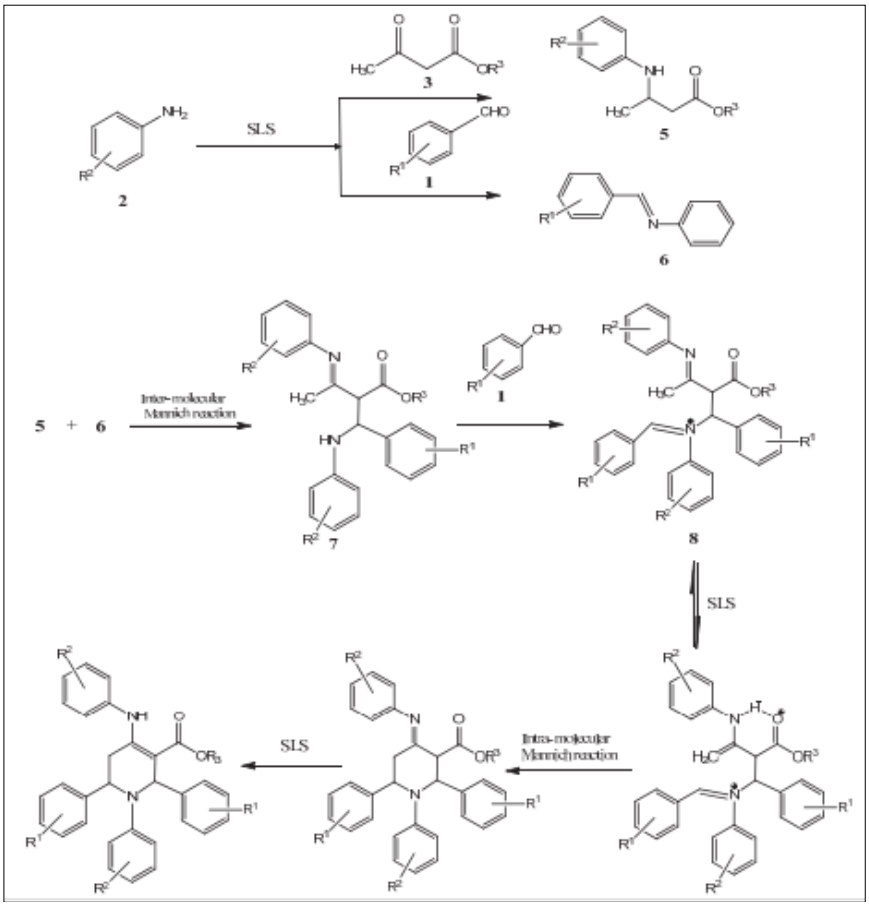
Entry	SLS, g	Time,h	Yield, %
1	0.005	6	20
2	0.01	6	30
3	0.02	6	95
4	0.05	6	30
5	0.10	6	N0 product

Conditions: benzaldehyde (2 mmol), aniline (2 mmol), ethyl acetoacetate (1 mmol), SLS (0.02 g), water (10 mL), room temperature

Based on previous literature records, it is reasonable to assume following mechanism of the reaction. Piperidines 4 results from initial condensation of aromatic aldehydes (1) and β-ketoesters (3) with anilines (2), in the presence of SLS, to give enamine (5) and imine (6) (Scheme 1A) which undergone intermolecular Mannich-type reaction to produce intermediate (7). The reaction between intermediate (7) and (1) gives intermediate 8 by the elimination of H2O. Tautomerization of (8) generates intermediate (9), which immediately undergoes intra-molecular Mannich-type reaction to give intermediate (10). Finally, the (10) tautomerizes to generate the desired piperidines derivative (4) owing to conjugation with the ester group.

This reaction can be regarded as an efficient approach for the preparation of synthetically and pharmaceuptically important piperidine systems.

In addition, we proposed the possibility for the formation of piperidines via double Mannich-type intermediates.



Scheme 1A: Proposed molecular mechanism

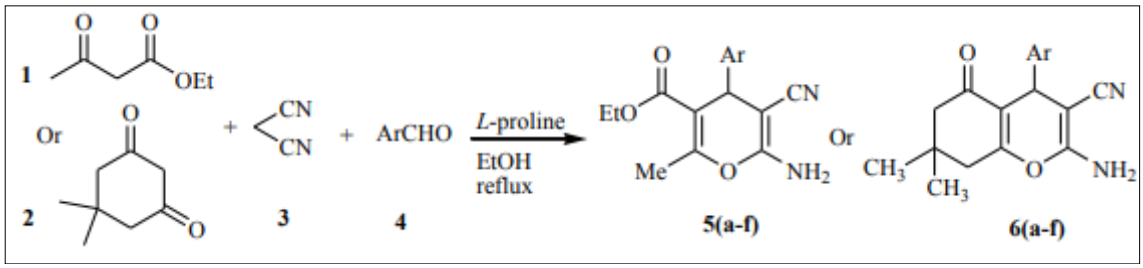
All the chemicals were received commercially and used without further purification. Melting points were determined in melting point apparatus, using open capillary tube and are uncorrected. NMR spectra were recorded with a Bruker AV III spectrometer at 400 MHz (1 H NMR) and 100 MHz (13C NMR) using CDCl3 as the solvent with tetramethylsilane (TMS) as internal standard. FT-IR spectra of compounds were recorded using KBr pellets on Shimadzu IR Affinity-1, Fourier-Transform infrared spectrometer.

A mixture of aromatic amine 2 (2 mmol) and β-ketoester 3 (1 mmol) in 10 ml water was stirred for 20 min in the presence of 0.02 g sodium lauryl sulfate at room temperature. Next the aromatic aldehyde 1 (2 mmol) was added and the reaction mixture was stirred for the time indicated in Table 2. The progress of reactions was monitored by thin layer chromatography (TLC), eluted with ethyl acetate and n-hexane (3:7) mixture. After completion of the reaction, a thick precipitate was filtered off and washed with water. The crystalline pure products were obtained by further recrystalization from ethanol.

One-pot synthesis of 2-amino-4h-pyrans and 2-amino-tetrahydro-4h-chromenes using l-proline

2-Amino-4H-pyran derivatives represent an important class of compounds which are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals. Poly functionalized 4H-pyrans also constitute a structural unit of many natural products and biologically interesting compounds which possess various pharmacological activities, such as anti-allergic, antitumor and antibacterial. 4H-Pyran derivatives are also potential calcium channel antagonists which are structurally similar to biologically active 1, 4- dihydropyridines.

Our recent interest has been in the development of new synthetic methods on using L-proline as bio and recyclable catalyst. In recent years, L-proline has gained importance as versatile catalyst for various organic transformations such as the synthesis of coumarins in ionic liquid and α-aminoxylation of aldehydes. Aso, L-proline and L-proline derivatives were successfully used as organo catalysts in asymmetric aldol and Michael addition reactions. To the best of our knowledge in the open literature, one- pot synthesis of 2-amino-4H-pyrans catalyzed by Lproline have not been reported. Therefore, we wish to report an efficient synthesis of 2-amino-4H-pyrans using of aromatic aldehydes, malononitrile and ethyl acetoacetate or dimedone by L-proline in ethanol under reflux conditions (Scheme 2). The advantages of this method are high reaction yields, short reaction times and use of ethanol as an environmentally friendly solvent.



Scheme 2: Synthesis of 2-amino-4-aryl-4H-pyrans or 2-amino-tetrahydro-4H-chromenes using L-proline

Firstly, the model reaction was simply carried out by mixing benzaldehyde, malononitrile, ethyl acetoacetate and L-proline in ethanol under reflux conditions. The corresponding ethyl 6-amino-5-cyano-2-methyl-4- phenyl-4H-pyran-3-carboxylate 5a was obtained in high yield. The effect of catalyst amount and different solvents such as ethanol, chloroform and water on the yield of product was evaluated (Table 4, 5).

Table 4: Solvent effecting on the synthesis of methyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate

Entry	Solvent(10 ml)	Yield%
1	CH_3Cl	55
2	C_2H_5OH	93
3	H_2O	88
4	C_2H_5OH:H_2O (1:1)	80
5	Solvent-free	68

Conditions: Benzaldehyde (1.0 mmol, 0.106 g), ethyl acetoacetate (1.0 mmol, 0.13 g), malonitrile (1.0 mmol, 0.066 g) and L-proline (10 mol%) under reflux conditions at 1.0 h.

As indicated in Table 4, the polar solvents such as ethanol were found much better than the non-polar solvents like chloroform. The results could be interpreted with the much better solubility the reactants in polar solvents. Thus in present study has been used only ethanol, which is relatively benign organic solvent and 10 mol% of L-proline as a reusable organo-catalyst.

Table 5: The effect of catalyst amount on the synthesis of methyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3- carboxylate

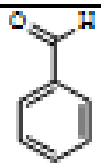
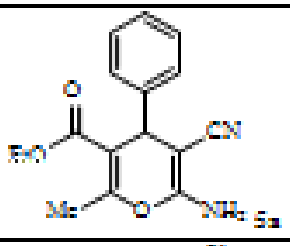
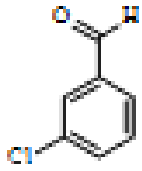
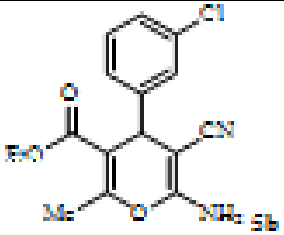
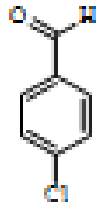
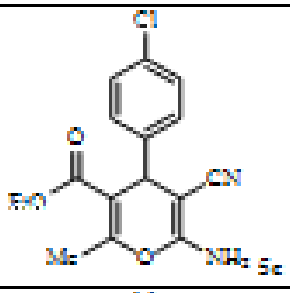
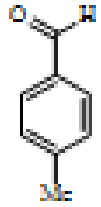
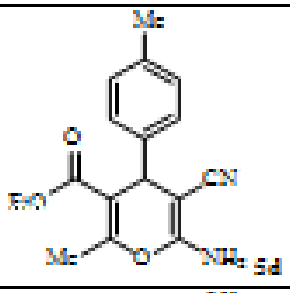
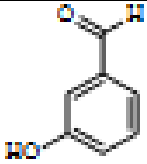
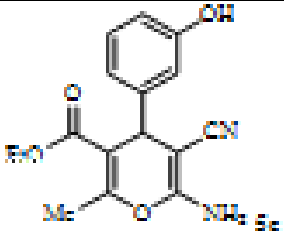
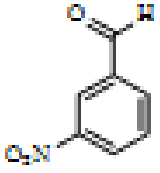
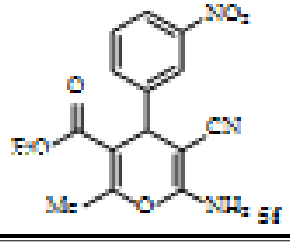
Entry	Catalyst (mol %)	Yield %[a]
1	Free	10
2	5	75
3	10	93
4	15	93

Conditions: Benzaldehyde (1 mmol, 0.106 g), ethyl acetoacetate (1 mmol, 0.13 g), malononitrile (1 mmol, 0.066 g) and L-proline (10 mol %) in ethanol (10 mL) under reflux conditions at 1.0h

However, the scope and generality of this three component one-pot synthesis of 2-amino-4H-pyrans have been illustrated with different aldehydes and the results have been summarized in Table 5. This method has the ability to tolerate a variety of other functional groups such as hydroxyl, methyl, nitro, and chloro under the reaction conditions. Both, the electron-rich and electron-deficient aldehydes worked well, leadgni to high yields of products 5a-f.

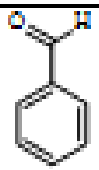
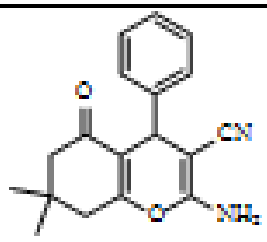
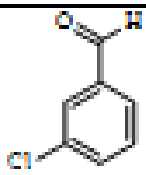
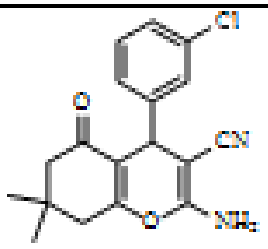
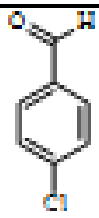
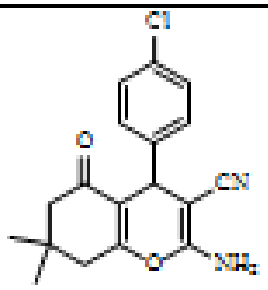
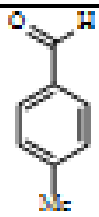
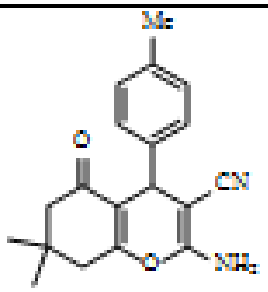
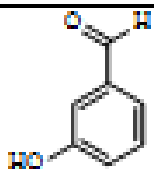
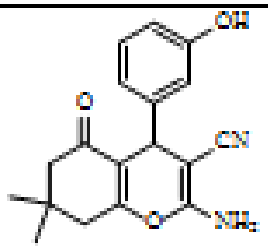
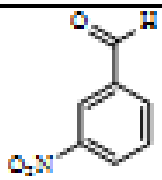
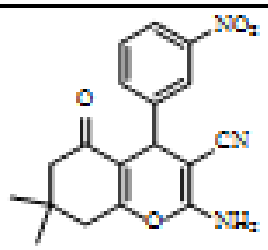
Also, in a series of reactions, dimedone was employed instead of ethyl acetate under reaction condition to give the corresponding or 2-amino-tetrahydro-4Hchromenes. In these cases, the reactions were then evaluated using a variety of structurally diverse aldehydes (Table 6). Three component condensation of dimedone with various aromatic aldehydes bearing electron withdrawing groups such as nitro or electron releasing groups such as methyl and malononitrile was carried out in the presence of L-proline as a catalyst. The yields obtained were good-to-excellent. The results obtained in the current method are illustrated in Table 5 (6a-f). In each case, the reaction profile is clean and this one-pot three-component procedure presents some improvements and advantages over existing methods. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple washing and crystallization of the crude products. All the products were identified by comparison of analytical data with those of authentic samples.

Table 6: Synthesis of 2-amino-4H-pyrans using L-proline

Entry	ArCHO	Product	Time(h)	Yield%	M.p.(°C) Found	Reported
1		 5a	1.0	84	194 -195	195-196[17]
2		 5b	2.0	78	152-154	153-156 [4]
3		 5c	2.0	72	170-171	172-174[18]
4		 5d	2.45	59	172-175	177-179 [18]
5		 5e	1.25	71	163-165	164-165 [18]
6		 5f	2.0	78	177-179	182-183 [4]

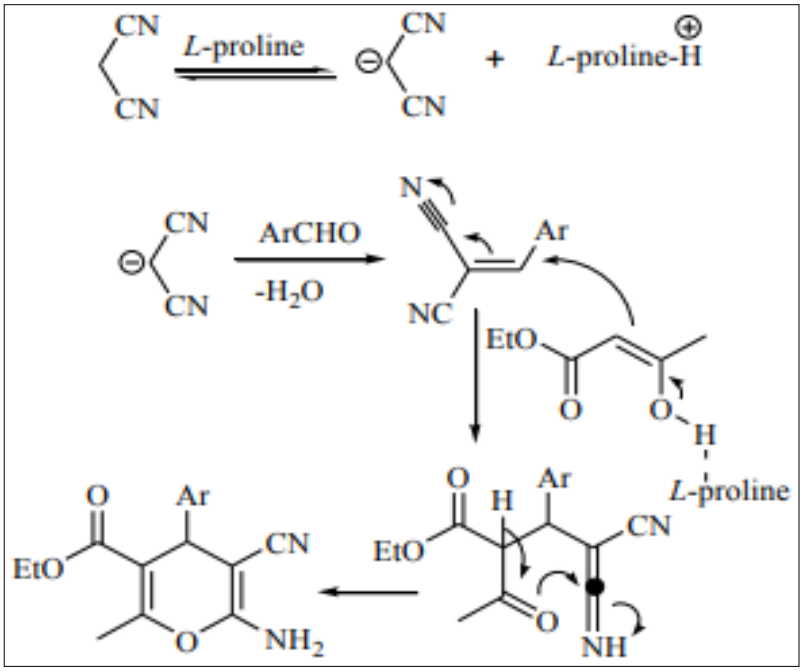
Conditions: Aryl aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol, 0.13 g), mononitrile (1.0 mmol, 0.066 g) and L-proline (10 mol %) in ethanol (10 mL) under reflux conditions

Table 7: Synthesis of 2-amino-tetrahydro-4H-chromenes using L-proline

Entry	ArCHO	Product	Time(h)	Yield%	M.p (°C) Found	M.p (°C) Reported
1		 6a	1.0	93	222-224	226-228 [9]
2		 6b	1.45	91	221-224	223-225[12]
3		 6c	1.5	87	199-202	202-203[10]
4		 6d	2.5	65	210	209-211[10]
5		 6e	2.0	79	219-221	224-226[10]
6		 6f	2.3	88	201-203	201-205[10]

Conditions: Aryl aldehyde (1.0 mmol), dimedone (1.0 mmol, 0.14 g), mononitrile (1.0 mmol, 0.066 g) and Lproline (10 mol %) in ethanol (10 mL) under reflux conditions

Mechanistically, the initial condensation of aromatic aldehyde with malononitrile in the presence of L-proline leads to the formation of arylidenemalononitrile with the loss of a water molecule. The nucleophilic addition of the enolizable ethyl acetoacetate to arylidene malononitrile followed by intramolecular cyclization of the resulting species produce the 2-amino-4H-pyrans (Scheme 2A).



Scheme 2A: Purposed mechanism for synthesis of 2-amino-4-aryl-4H-pyrans or 2-amino-tetrahydro-4H-chromenes using L-proline

Conclusion

Nitrogen-based heterocyclic chemistry is a unique and important branch of organic chemistry that has gained a lot of interest recently. The development of new structures for this class of molecules has received a lot of attention. A general methodology of the formation of highly functionalized piperidines from commonly available starting materials, in presence of catalytic amounts of sodium lauryl sulfate, via one-pot three component reaction is reported. The salient features of this protocol are good yields, mild reaction conditions, environment friendly, superior atom economy and the readily accessibility of the catalyst.

Also, a facile, convenient and environmentally benign one-pot synthesis of 2-amino-4H-pyrans and 2- amino-tetrahydro-4H-chromenes have developed using L-proline-in ethanol under reflux conditions. The desired products can be also obtained in high yields and purities without further chromatographic purification.

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