Asian Journal of Green Chemistry 7 (2023) 121-131

Asian Journal of Green Chemistry

Original Research Article

View Article Online | View Journal

L-Proline Catalyzed Multicomponent Reaction for Simple and Efficient Synthesis of Tetrahydropyridines Derivatives

Raad Muslim Muhiebes [a,*], Leila Fatolahi [b], Sami Sajjadifar [b]

[a] *Department of Biochemistry, College of Medicine, Missan University, Missan, Iraq*

[b] *Department of Chemistry, Payame Noor University, PO BOX 19395-4697 Tehran, Iran*

ARTICLE INFORMATION

Received: 18 February 2023
Received in revised: 26 April 2023
Accepted: 29 April 2023
Available online: 3 May 2023

Manuscript ID: AJGC-2304-1380
Checked for Plagiarism: Yes
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Sobhan Rezayati

DOI: 10.22034/ajgc.2023.393683.1380

KEYWORDS

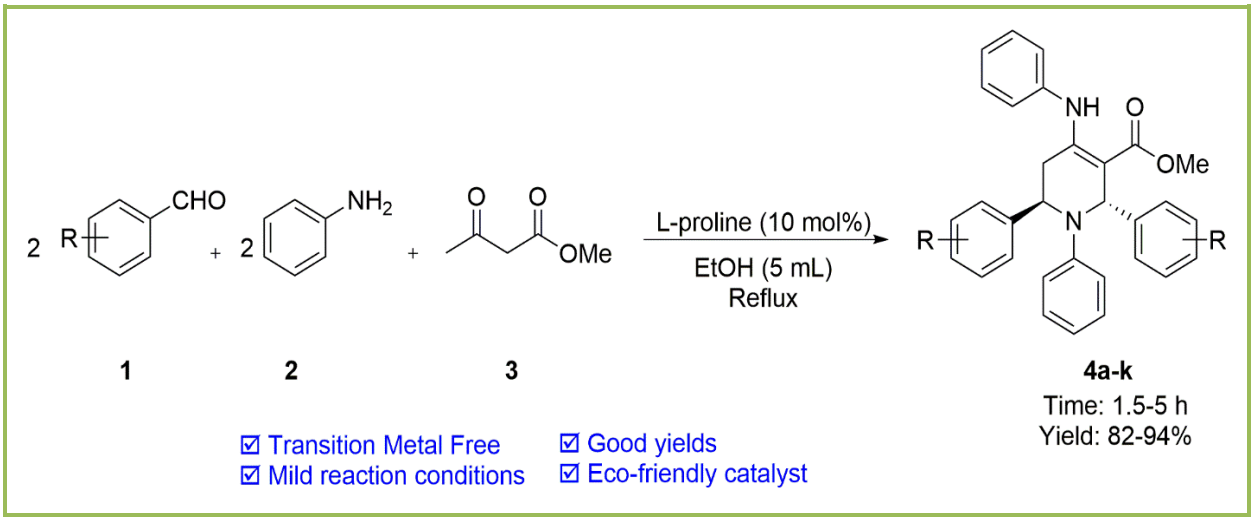
L-Proline
Tetrahydropyridines derivatives
MCRs
Organo-catalyst

ABSTRACT

In this study, L-Proline as an organo-catalyst has been used for the synthesis of highly functionalized tetrahydropyridines derivatives in good to excellent yields by one-pot multicomponent reaction (MCR) of aniline, methyl acetoacetate, and aromatic aldehydes in ethanol under reflux conditions. The use of green solvents, eco friendliness, mild reaction conditions, and low catalyst loading are advantages of current study.

Corresponding authors, email: Raadmuslim7@gmail.com (R. Muslim Muhiebes).

Graphical Abstract



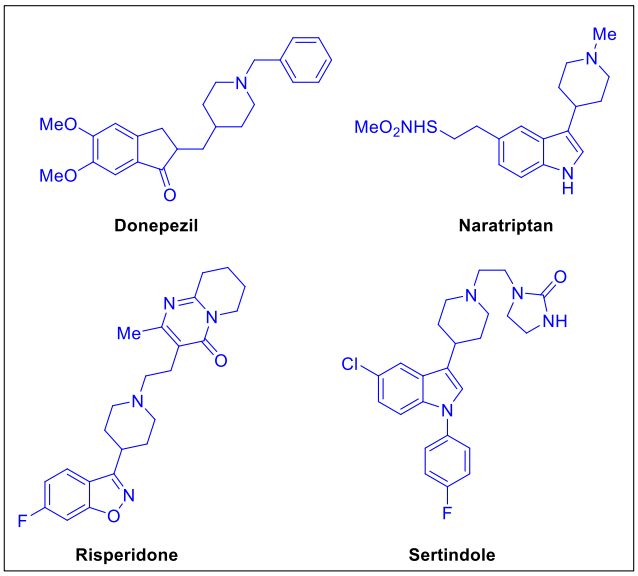
Introduction

Due to the complexity and variety of organic synthesis, multicomponent reactions (MCRs) are gaining favorable attention [1-4]. MCRs are described as a one-pot procedure that entails at least three components reacting to produce a single product that virtually contains every atom of the starting elements. As a result, theoretically, a variety of sets of reasonably intricate structures could be produced from fundamental building blocks in a single reaction step. MCRs extensively has been used for preparation of agrochemicals, drug development, and organic synthesis [5-11]. One of the most important carbon-carbon and carbon-heteroatom bonds forming reactions in organic synthesis to make the biological and medicinal compounds are tetrahydropyridines derivatives.

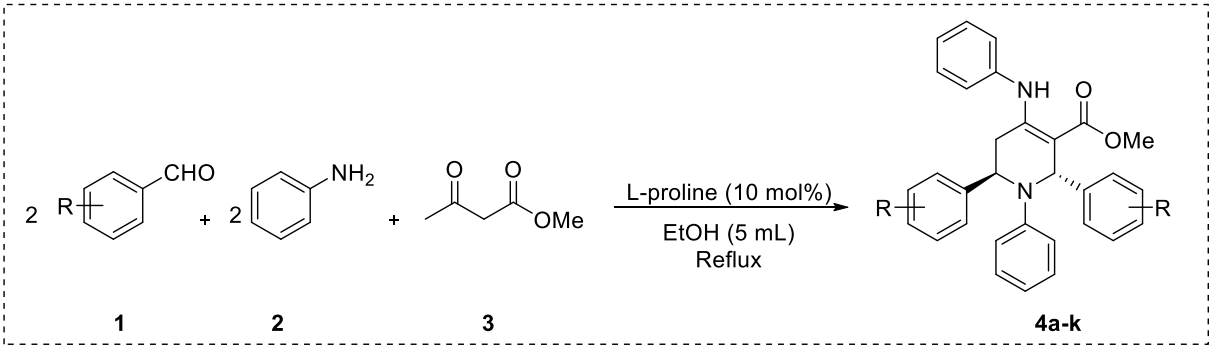
One of the most significant compounds in organic chemistry and natural products are tetrahydropyridines and its analogues. These compounds are synthesized by applying MCRs exhibit special biological and medicinal activities such as anti-inflammatory activities [12], anti-bacterial [13], and anti-hypertensive [14]. Scheme 1 illustrates some Piperidine scaffolds that have role in commercially available drugs such as Sertindole and Risperidone (for schizophrenia treatment of), Naratriptan (for the treatment of migraine headaches), and Donepezil (for the treatment of Alzheimer's disease) [15-18].

Recently, various catalysts are widely applied for the synthesis of tetrahydropyridines using MCRs, such as ionic liquid [19], $InCl_3$ [20], $ZrCl_4$ [21], $FeCl_3/SiO_2$ NPs [22], PEG-embedded KBr_3 [23], chiral phosphoric acids [24, 25], CAN [26], acetic acid [27], picric acid [28], $ZrOCl_2.8H_2O$ [29], BF_3/SiO_2 [30], and TBATB [31]. Some of reported procedures suffer from disadvantages including use of toxic solvents, poor yields, expensive reagents, and long reaction time.

Given the interesting advantages of MCRs or recent developments in nanomaterial synthesis in catalysis science [32-41], herein, we used L-Proline as an organo-catalyst for the synthesis of tetrahydropyridines derivatives from amines, methyl acetoacetate, and aromatic aldehydes in ethanol at room temperature (Scheme 2).



Scheme 1. Some Piperidine scaffolds that have role in commercially available drugs



Scheme 2. L-Proline catalyzed synthesis of tetrahydropyridines derivatives

Experimental

General procedure for the preparation of tetrahydropyridines derivatives

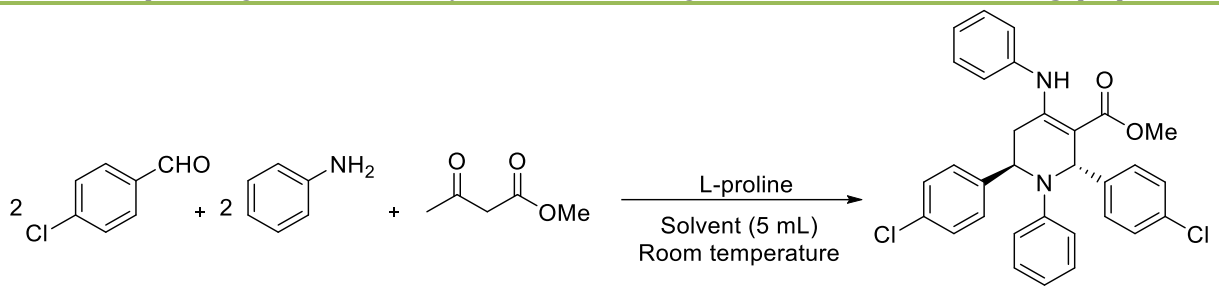
The mixture of aromatic aldehyde (2 mmol), methyl acetoacetate (1 mmol), aniline (2 mmol), and L-proline (10 mol%) in ethanol (5 mL) for synthesis of products **4a-b** was stirred under reflux conditions for the appropriate times. Reaction progress was investigated using TLC. After completion of the reaction, 20 mL ethyl acetate was added to reaction mixture to diluted, and then the reaction mixture washed with water and brine and dried through anhydrous Na_2SO_4. Finally, pure products were prepared via silica gel column chromatography.

Results and Discussion

To optimize the synthesis of tetrahydropyridines derivatives, the effect of different parameters for instance solvent and loading of catalyst was studied in the reaction of aniline, methyl acetoacetate, and 4-chlorobenzaldehyde as a model reaction (Table 1). To explore the catalyst effect, the model reaction was performed with various amount of catalyst such as 1-15 mol% at room temperature in ethanol (Table 1, entries 2-8).

As listed in Table 1, good yield (95%) was obtained in a short reaction time (2.5 h) compared to the other temperatures in the attendance of 10 mol% of catalyst at room temperature (Table 1, entry 6). In another study, to explore the solvent effect, the model reaction was performed with various solvents, including MeOH, MeCN, THF, CH_2Cl_2 and water (Table 1, entries 9-13). As can be seen, the ethanol effect is betters than the other solvents.

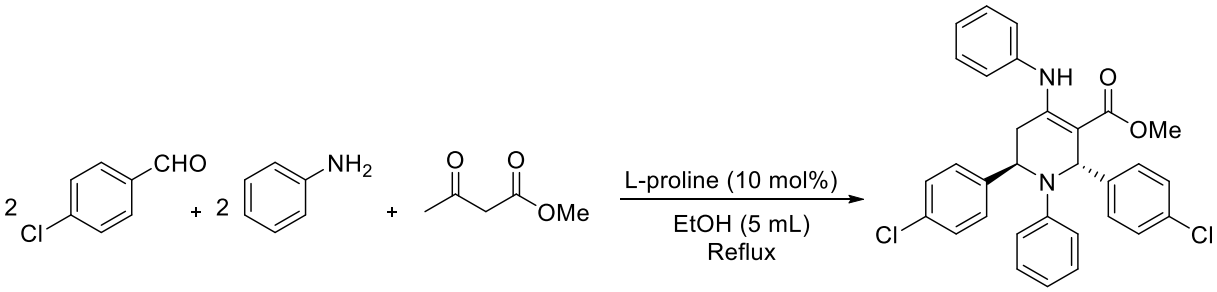
Table 1. Optimizing the solvent, catalyst amount according to the model reaction for the **4g**[a] preparation



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	-	-	12	0
2	1	EtOH	7	31
3	3	EtOH	6	53
4	5	EtOH	6	71
5	7	EtOH	5	79
6	10	EtOH	3	85
7	12	EtOH	3	84
8	15	EtOH	3.5	81
9	10	MeOH	3	65
10	10	MeCN	15	Trace
11	10	THF	12	21
12	10	CH_2Cl_2	12	Trace
13	10	Water	18	Trace

[a]Reaction conditions: 4-chlorobenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), solvent (5 mL), and L-proline at room temperature
[b] Isolated yield

Table 2. Optimizing the temperature according to the model reaction for the **4g** preparation[a]



Entry	Temperature (°C)	Time (h)	Yield (%)
1	Room temperature	3	85
2	40	3	85
3	60	2.5	89
4	Reflux	2.5	93

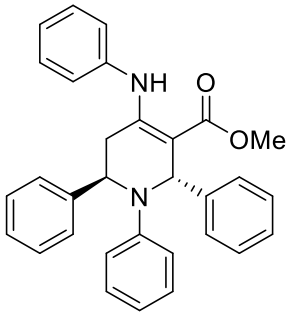
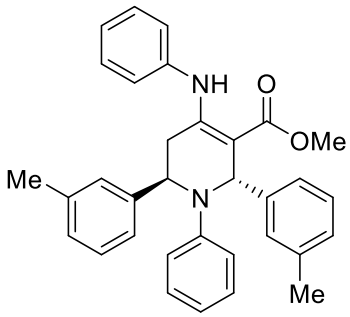
[a]Reaction conditions: 4-chlorobenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), EtOH (5 mL), and L-proline (10 mol%) under reflux conditions

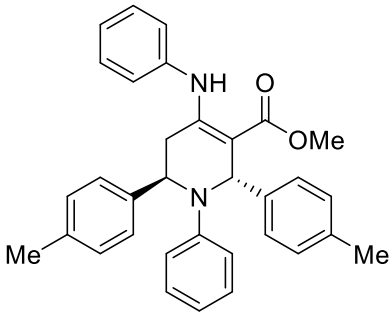
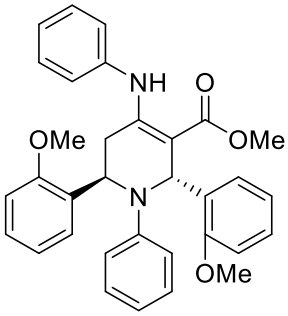
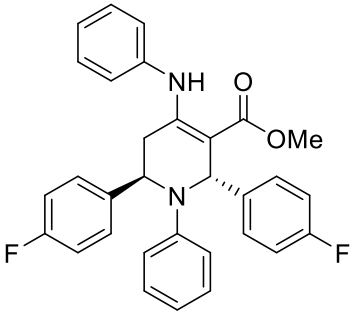
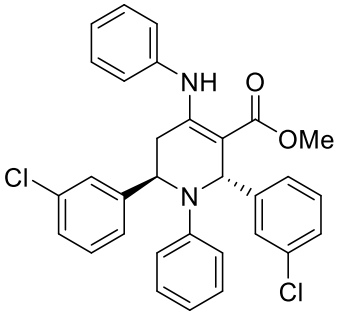
The effect of temperature was also perused onto the model reaction was studied. For this purpose, the reaction carried out in the presence of 10 mol% of catalyst in EtOH various temperature. Reaction performance with various temperatures including room temperature, 40, 60 and reflux conditions was performed to explore the temperature effect (Table 2, entries 1-4). As presented in Table 2, good yield (95%) was obtained in a short reaction time (2.5 h) for reflux conditions compared to the other temperatures listed in the table (Table 2, entry 4). The obtained optimized condition for the synthesis of compound 4g was the use of 10 mol% of L-Proline in ethanol under reflux condition.

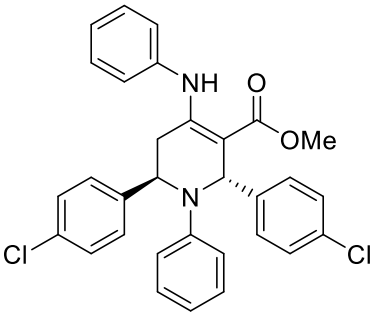
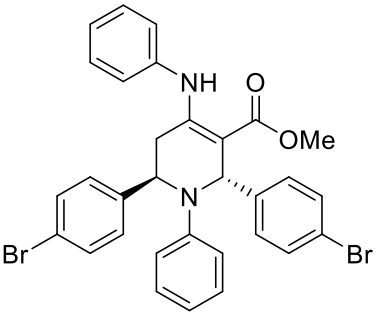
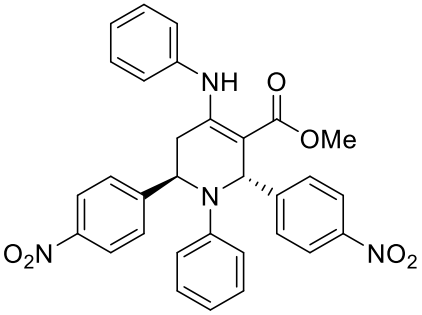
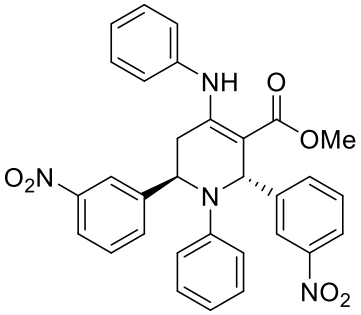
Preparation of tetrahydropyridines derivatives **4a-k** were studied using a series of amines, methyl acetoacetate, and aromatic aldehydes in ethanol under reflux conditions to evaluate generality and applicability of this method, and the results summarized in Table 3. As indicated in Table 3, all aromatic aldehydes including aldehydes have led synthesizing of corresponding tetrahydropyridines derivatives in high to excellent yield and no side products have been observed.

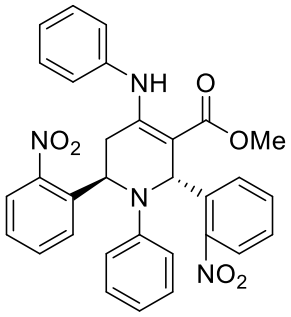
Scheme 3 represents a mechanism to afford tetrahydropyridines derivatives in the attendance of L-Proline as an organo-catalyst.

Table 3. Preparation of tetrahydropyridines derivatives catalyzed by L-Proline

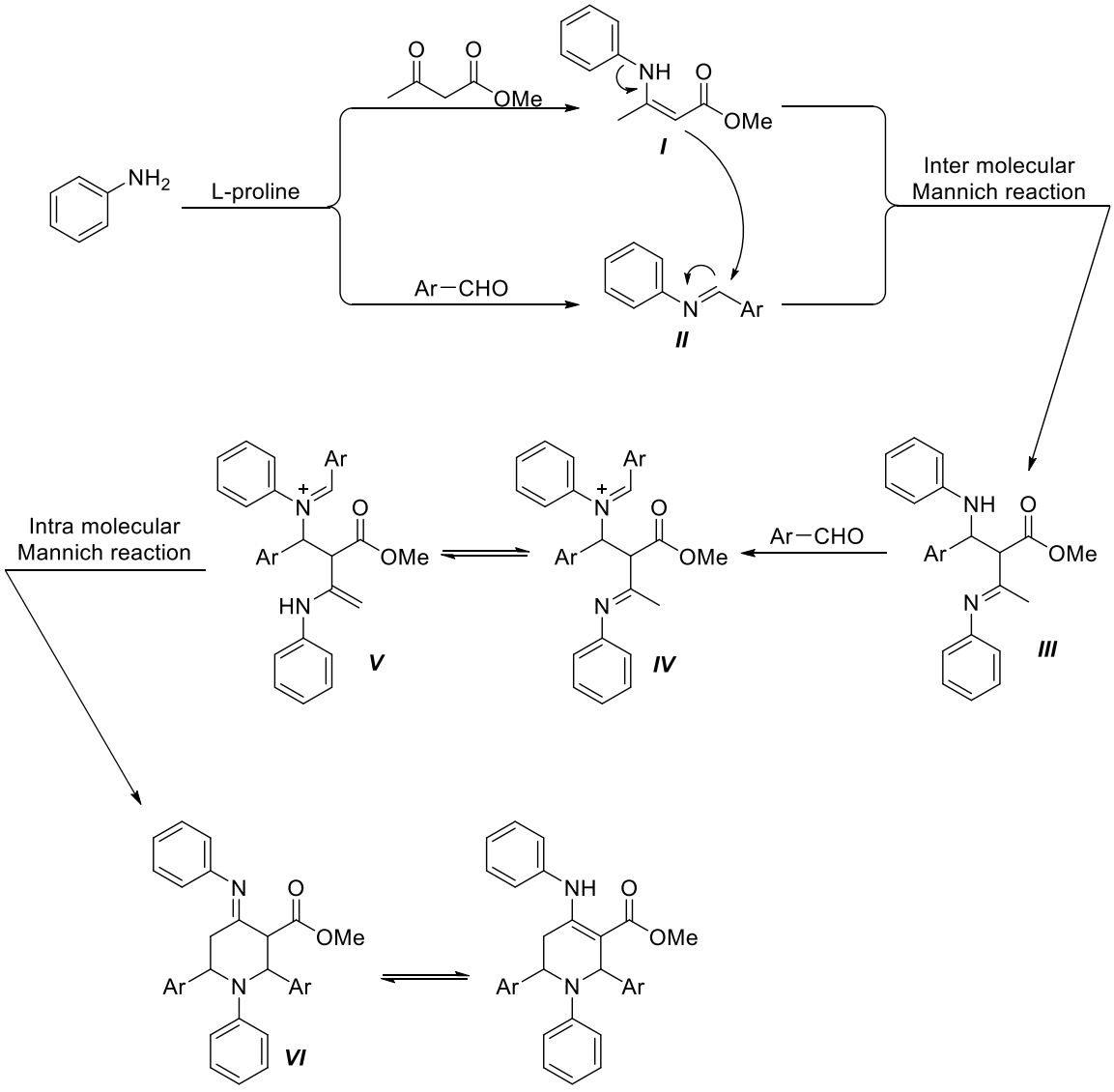
Entry	Product	Time (h)	Yield (%)	Mp (reference)
1	 **4a**	2.5	93	192-194 [42]
2	 **4b**	3.5	90	130-132 [42]

3	 **4c**	3	88	212-214 [42]
4	 **4d**	5	86	249-252 [42]
5	 **4e**	2.5	90	159-161 [42]
6	 **4f**	3.5	92	221-223 [42]

7	 **4g**	1.5	94	226-228 [42]
8	 **4h**	1.5	92	244-246 [42]
9	 **4i**	3.5	91	238-240 [42]
10	 **4j**	5.5	85	179-182 [42]

11	 **4k**	4	82	180-182 [42]

[a]Reaction conditions: Various aldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), EtOH (5 mL), and L-proline (10 mol%) under reflux conditions
[b] Isolated yield



Scheme 3. Plausible reaction mechanism of tetrahydropyridines derivatives

Conclusion

In conclusion, we have developed a green and simple reaction of amines, methyl acetoacetate, and aromatic aldehydes catalyzed by from L-Proline. This method provides access to tetrahydropyridines derivatives in excellent yields and short reaction time.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Orcid

Raad Muslim Muhiebes
https://orcid.org/0000-0003-0181-5837
Leila Fatolahi
https://orcid.org/0000-0002-7282-0601
Sami Sajjadifar
https://www.orcid.org/0000-0001-8661-1264

References

[1]. Ugi I. *Pure Appl. Chem*. 2001, **73**:187 [Crossref], [Google Scholar], [Publisher]
[2]. Hajinasiri R., Rezayati S. *Zeitschrift für Naturforschung B*, 2013, **68**:818 [Crossref], [Google Scholar], [Publisher]
[3]. Ramo´n D.J., Yus M. *Angew. Chem. Int. Ed.* 2005, **44**:1602 [Crossref], [Google Scholar], [Publisher]
[4]. Pagore V.P., Jadhav V.B., Bajad P.N., Pawar R.P. *Asian Journal of Green Chemistry,* 2020, **4**:379 [Crossref], [Publisher]
[5]. Ghafuri H., Zargari M., Emami A. *Asian Journal of Green Chemistry*, 2023, **7**:54 [Crossref], [Publisher]
[6]. Muslim Mhaibes R., Arzehgar Z., Mirzaei Heydari M., Fatolahi L. *Asian Journal of Green Chemistry*, 2023, **7**:1 [Crossref], [Publisher]
[7]. Baghernejad B., Hojjati Taromsari S.M. *Asian Journal of Green Chemistry*, 2022, **6**:194 [Crossref], [Publisher]
[8]. Shkyair Lihumis H., Abbas Al Talebi Z., Hussein Shanan S. *Asian Journal of Green Chemistry*, 2022, **6**:68 [Crossref], [Publisher]
[9]. Khanivar R., Zare A., Sadeghi-Takallo M. *Asian Journal of Green Chemistry*, 2021, **5**:1 [Crossref], [Publisher]
[10]. Singha R., Brahman D., Sinha B., Ghosh P. *Asian Journal of Green Chemistry*, 2021, **5**:91 [Crossref], [Publisher]
[11]. Baghernejad B., Salimifar S. *Asian Journal of Green Chemistry*, 2021, **5**:196 [Crossref], [Publisher]
[12]. Bin H., Crider A.M., Stables J.P. *Eur. J. Med. Chem*., 2001, 36:265 [Crossref], [Google Scholar], [Publisher]
[13]. Zhou Y., Gregor V.E., Ayida B.K., Winters G.C., Sun X., Murphy D., Haley G., Bailey D., Froelich J.M., Fish S., Webber S.E., Hermann T., Wall D. *Bioorg. Med. Chem. Lett*., 2007, **17**:1206 [Crossref], [Google Scholar], [Publisher]
[14]. Petit S., Nallet J.P., Guillard M., Dreux J., Chermat R., Poncelet M., Bulach C., Simon P., Fontaine C., Barthelmebs M., Imbs J.L. *Eur. J. Med. Chem*., 1991, **26**:19 [Crossref], [Google Scholar], [Publisher]
[15]. Yevich J.P., Yocca F.D. *Curr. Med. Chem*., 1997, **4**:295 [Google Scholar], [Publisher]
[16]. Yamanishi Y., Ogura H., Kosasa T. *Tanpakushitsu Kakusan Koso*, 2000, 45:1047 [Google Scholar], [Publisher]

[17]. Targum S., Zboroaski J., Henry M., Schmitz P., Sebree T., Wallin B. *Eur. Neuropsychopharmacol*., 1995, **5**:4 [Google Scholar], [Publisher]
[18]. Schotte A., Janssen P.F.M., Gommeren W., Luyten W.H.M.L., van Gompel P., Lasage A.S., De Loore K., Leysen J.E. *Psychopharmacology*, 1996, **57**:124 [Crossref], [Google Scholar], [Publisher]
[19]. Sajadikhah S.S., Hazeri N., Maghsoodlou M.T., Habibi-Khorassani S.M., Beigbabaei A., Lashkari M. *J. Chem. Res*. 2012, **36**:463 [Google Scholar], [Publisher]
[20]. Clarke P.A., Zaytzev A.V., Whitwood A.C. *Tetrahedron Lett*., 2007, **48**:5209 [Crossref], [Google Scholar], [Publisher]
[21]. R. Aeluri, M. Alla, V.R. Bommena, R. Murthy, N. Jain, Asian J. Org. Chem. 1, 71 (2012) [Crossref], [Google Scholar], [Publisher]
[22]. Ghomi J.S., Ziarati A. *J. Iran. Chem. Soc*., 2013, **10**:135 [Crossref], [Google Scholar], [Publisher]
[23]. Verma S., Jain S.L., Sain B., *Beilstein J. Org. Chem*., 2011, **7**:1334 [Crossref], [Google Scholar], [Publisher]
[24]. Shi F., Tan W., Zhu R.Y., Xing G.J., Tua S.J. *Adv. Synth. Catal*., 2013, 355:1605 [Crossref], [Google Scholar], [Publisher]
[25]. Li X., Zhao Y., Qu H., Mao Z., Lin X. *Chem. Commun*. 2013, **49**:1401 [Crossref], [Google Scholar], [Publisher]
[26]. Wang H.J., Mo L.P., Zhang Z.H. *ACS Comb. Sci*., 2011, **13**:181 [Crossref], [Google Scholar], [Publisher]
[27]. Lashkari M., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Sajadikhah S.S., Doostmohamadi R. *Synth. Commun*. 2013, **28**:635 [Crossref], [Google Scholar], [Publisher]
[28]. Mukhopadhyay C., Rana R., Butcher R.J., Schmiedekamp A.M. *Tetrahedron Lett*., 2011, **52**:5835 [Crossref], [Google Scholar], [Publisher]
[29]. Mishra S., Ghosh R. *Tetrahedron Lett*., 2011, **52**:2857 [Crossref], [Google Scholar], [Publisher]
[30]. Ramachandran R., Jayanthi S., Jeong Y.T. *Tetrahedron*, 2012, **68**:363 [Crossref], [Google Scholar], [Publisher]
[31]. Khan A.T., Lal M., Khan M.M. *Tetrahedron Lett*., 2010, **51**:4419 [Crossref], [Google Scholar], [Publisher]
[32]. Sajjadifar S., Fadaeian M., Bakhtiyari M., Rezayati S. *Chem Sci Trans*., 2014, **3**:107 [Google Scholar], [Publisher]
[33]. S. Rezayati, S. Sajjadifar. *Journal of Sciences, Islamic Republic of Iran*, 2014, **25**:329 [Crossref], [Publisher]
[34]. Sajjadifar S., Rezayati S. *International Journal of ChemTech Research*, 2013, 5:1964 [Publisher]
[35]. Rezayati S., Ramazani A., Sajjadifar S., Aghahosseini H., Rezaei A. *ACS Omega,* 2021, **6**:25608 [Crossref], [Google Scholar], [Publisher]
[36]. Sajjadifar S., Rezayati S., Shahriari A., Abbaspour S. *Applied Organometallic Chemistry*, 2018, **32**:e4172 [Crossref], [Google Scholar], [Publisher]
[37]. Sajjadifar S., Rezayati S., Arzehgar Z., Abbaspour S., Torabi Jafroudi M. *Journal of the Chinese Chemical Society*, 2018, **65**:960 [Crossref], [Google Scholar], [Publisher]
[38]. Rezayati S., Kalantari F., Ramazani A., Sajjadifar S., Aghahosseini H., Rezaei A. *Inorg. Chem*. 2022, **61**:992 [Crossref], [Google Scholar], [Publisher]
[39]. Rezayati S., Sajjadifar S., Hajinasiri R. *Iranian Journal of Science & Technology*. 2015, **39A2**:179 [Google Scholar], [Publisher]
[40]. Taherkhani H., Ramazani A., Sajjadifar S., Aghahosseini H., Rezaei A., Rezayati S. *ChemistrySelec*t, 2021, **6**:11362 [Crossref], [Google Scholar], [Publisher]
[41]. Rezayati S., Dinmohammadi G., Ramazani A., Sajjadifar S. *Polycyclic Aromatic Compounds*,

2022, DOI: 10.1080/10406638.2022.2110506 [Google Scholar], [Publisher]
[42]. Wang H.H., Mo L.P., Zhang Z.H. *ACS Comb. Sci*., 2011, **13**:181 [Crossref], [Google Scholar], [Publisher]

How to cite this manuscript: Raad Muslim Muhiebes*, Leila Fatolahi, Sami Sajjadifar**.** L-Proline Catalyzed Multicomponent Reaction for Simple and Efficient Synthesis of Tetrahydropyridines Derivatives. *Asian Journal of Green Chemistry*, 7(2) 2023, 121-131. DOI: 10.22034/ajgc.2023.393683.1380