Think India Journal
ISSN: 0971-1260 Vol-22, Special Issue-31
National Conference ETDAB-2019
Held on 23th & 24th December 2019
Organized by: Deptt. of Botany, Deogiri College, Aurangabad, M.S

An Efficient L-Proline Promoted Synthesis And Antimicrobial Study Of 2,5-Disubstituted-1,3,4-Oxadiazoles

A. V. Nakhate[1*], S. V. Shinde[2]
[1]Marathwada Institute of Technology, Aurangabad – 431010.
[2]Pratibha Niketan College, Nanded – 431604
*Email : arjun108vnakhate@gmail.com

Abstract:

A series of 2,5-disubstituted-1,3,4-oxadiazole and its derivatives were synthesized. The oxadiazole derivatives were synthesized by the reaction of aromatic aldehydes and acyl hydrazides in the presence of L-proline. The method has wide advantages over existing methodologies. The synthesized oxadiazole compounds were screened for their antimicrobial activities, some compounds shows very good activities.

Keywords: Oxadiazole, L-proline, antibacterial, antifungal.

Introduction:

The five membered heterocyclic compounds which contains nitrogen and oxygen atom in their cyclic rings attains considerable importance due to their prevalence in natural products[1] also because of their interesting pharmacological properties[2]. They also possess optoelectronic and photochemical properties[3]. In particularly, heterocyclic compounds of five membered rings are of great interest due to its inherent biological activity[4]. Considering the importance of oxadiazole and its derivatives are the privileged scaffolds in different areas of material science, pesticidal, polymer and medicinal[5]. Some oxadiazole derivatives acts as an anticancer, benzodiazepine receptor agonists, analgesic, antimicrobial, diuretic and tyrosinase inhibitos[6]. Some newly synthesized oxadiazole derivatives are in late stage clinical trials including zibotental and furamizole. On the other side, an anti-retroviral drug for the treatment of HIV infection, has been launched into the pharmaceutical market[7].

Many synthesis methods are available for 2,5-disubstituted-1,3,4-oxadiazole and derivatives which includes an oxidative cyclization of N-acyl-N[l]-aryliden-hydrazines promoted by an excess of Dess-Martin reagent under mild conditions[8], bis(trifluoraocetoxy)iodobenzene[9], DDQ[10], TsCl[11], CuI[12], 110eric ammonium nitrate[13], I_2[14], $POCl_3$[15].

The literature survey reveals that 2,5-disubstituted-1,3,4-oxadiazole and derivatives has wide range of applicability, so many methods are available for its synthesis but consist some drawback also such as use of hazardous chemical, time consuming method, lower yields. To overcome these, there is need to develop new methods which minimizes these drawbacks and in present study we developed such methods to synthesis 2,5-disubstituted-1,3,4-oxadiazoles by refluxing aromatic aldehydes and acyl hydrazide in presence of L-proline as a catalyst.

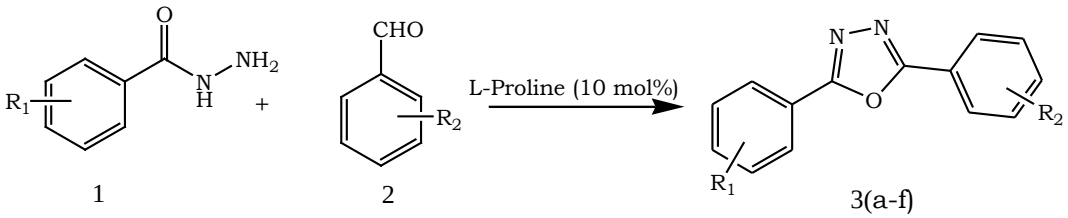
Material & Methods:

The chemicals are purchased from s. d. fine limited, Aldrich and Rankem and are used without further purification. The identification and purity of the products were checked by TLC (Ethyl acetate: acetone, 9:1). The melting points were measured on open capillaries in a liquid paraffin bath and are uncorrected. The Infra red spectra were taken on FTIR-Jasco using potassium bromide pellets. 1H NMR spectra were recorded in DMSO-d6 on AMX-400, NMR spectrometer using TMS as an internal standard.

General Procedure for the synthesis of 2,5-disubstituted oxadiazoles

A mixture of aromatic aldehyde (1 mmol), acyl hydrazide (1 mmol) and L-proline (10 mol%) in ethanol (20mL) was stirred at reflux temperature for 2-3 h. the progress of the reaction was monitored by TLC. After completion of reaction conversion, the reaction mixture was cooled at room temperature and poured on crushed ice. The obtained crude solid product was filtered, dried and recrystallized from ethanol to get corresponding 2,5-disubstituted-1,3,4-oxadiazoles.

Think India Journal
ISSN: 0971-1260 Vol-22, Special Issue-31
National Conference ETDAB-2019
Held on 23th & 24th December 2019
Organized by: Deptt. of Botany, Deogiri College, Aurangabad, M.S



Results & Discussion:

In continuation of our research work on the development of synthetic methodologies, we would like to report a highly efficient route for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles catalyzed by an commercially available, inexpensive, mild organocatalyst L-proline. This protocol is a coupling of benzaldehyde and acyl hydrazide in ethanol. In our search for the better solvent and the best experimental reaction conditions in the preparation of 2,5-disubstituted-1,3,4-oxadiazoles.

We have determined that the reaction of benzaldehyde and acyl hydrazide in ethanol at reflux is the standard model reaction. To evaluate the effect of solvent, we have screened different solvents such as dichloromethane, tetrahydrofuran, acetonitrile, chloroform, dioxane, methanol, 2-propanol and ethanol at reflux temperature, ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (91%) of desired product, whereas the product formed in lower yields (39 to 86%) by using other solvents [Table 1, entries 1 – 7]. In case of the protic solvents the yields are better than aprotic solvents [Table 1, entries 6-8].

We screened a number of different catalysts such as glycine, 3-aminopropanoic acid affords the desired product in low yields 82 and 86% respectively [Table 2, entries 2, 3]. However, L-proline provided the best results yielding 91% of product within 2.5 hr [Table 2, entry 4].

To determine the role of catalyst, the same reaction was carried out in the absence of catalyst, which resulted in 37% yield formation after 4 hrs. These results indicate that catalyst exhibits a high catalytic activity in this transformation.

To determine the optimum concentration of catalyst, we have investigated the model reaction at 5, 7.5, 10 and 12.5 mol% of L-proline in ethanol at reflux temperature. The product was obtained in 83, 87, 91 and 91%yield respectively, this indicate that the use of 10 mol% of L-proline is sufficient to promote the reaction forward (Table 3).

To study the generality of this process, variety of examples were illustrated for the synthesis of 2,5-disubstitues-1,3,4-oxadiazoles and results are summarized in Table 4. The reaction is compatible for various substituents. The formation of desired product was confirmed by 1H NMR, IR and Mass spectroscopic analysis technique. Also the melting points were recorded and compared with the corresponding literature data.

Table 1. Screening o solvents for the synthesis of compound[a].

Entry	Solvent	Yield[b] (%)
1	Dioxane	39
2	Acetonitrile	41
3	Tetrahydrofuran	47
4	Dichloromethane	55
5	Chloroform	58
6	Methanol	79
7	2-propanol	86
8	Ethanol	91

1. Reaction condition: 1[a] (1 mmol), 2 (1 mmol), L-proline (10 mol%) at reflux temperature. [b]- Isolated yields.

Table 2. Screening of catalyst for the synthesis of compound[a] 3a.

Entry	Catalyst	Time (Hrs)	Yield[b](%)
1	Without catalyst	4	37
2	Glycine	3	82
3	3-aminopropanoic acid	2.5	86
4	L-proline	2.5	91

2. Reaction condition: 1[a] (1 mmol), 2 (1 mmol), L-proline (10 mol%) at reflux temperature. [b]- Isolated yields.

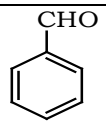
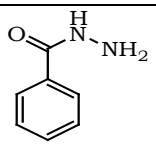
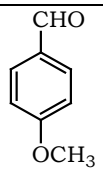
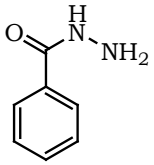
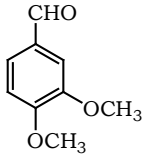
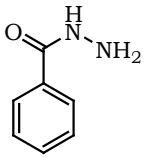
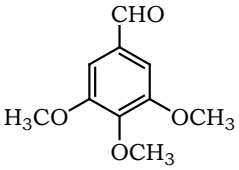
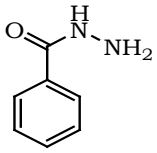
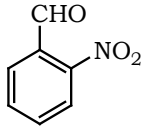
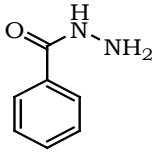
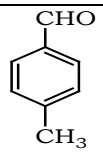
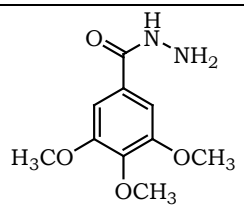
Table 3: Effect of concentration of L-proline[a].

Entry	Concentration (mol%)	Yield[b] (%)
1	5	83
2	7.5	87
3	10	91
4	12.5	91

3. Reaction condition: 1[a] (1 mmol), 2 (1 mmol), L-proline (10 mol%) at reflux temperature. [b]- Isolated yields.

Table 4: L-proline catalyzed synthesis of 2,5-disubstituted-1,3,5-oxadiazoles.

Entry	Aryl Aldehyde	Aryl Hydrazide	Time (h)	Yield (%)	M.P. (ºC)[a]

3a			2.5	91	136-137
3b			2,6	87	95-96
3c			2.3	86	107-108
3d			2.5	85	121-122
3e			2.8	87	190-192
3f			2.6	85	122-123

[a]-all products are known and IR, NMR values matched with authentic data.

Antimicrobial activity of the synthesized compounds was tested against three bacterial strains using agar well diffusion method. Dimethylsulfoxide (DMSO) was used as a solvent control. The bacterial cultures were inoculated on nutrient agar (Merck) and fungal culture was inoculated on potato dextrose agar media (20 mL). The synthesized compounds were dissolved in DMSO to get concentration of 11.28 M, and 100µl of this sample loaded into the wells of agar

plates directly. These Plates were inoculated with the bacteria at 37 C for 24 hrs and the fungal culture was incubated at 25 C for 72 hrs. The results are shown in Table 5.

Table 5. Antibacterial and antifungal activity of compounds.

Antibacterial (Zone of inhibition in mm)				Antifungal (Zone of inhibition in mm)		
Compound	Ecoli	Salmonella typhi	Bacillus substitus	Aspergillus Niger	Asp. Flavus	Asp.chryso genum
3a	8	9	9.5	13	12	12
3b	7	7	8	11	12.5	9
3c	8.5	8	6	14	12	11
3d	10	11	8.5	13	9.5	11
3e	6	8	8	12	10	8.5
3f	4.5	7	6	8	10.5	11
Streptomycin	16	14	14	Fluconazole, 18	16	18

Conclusions:

In conclusion, we have developed a simple, safe and green methodology for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles from the condensation of aromatic aldehydes and acyl hydrazide in the presence of L-proline as a catalyst in ethanol medium at room temperature. The notable merits offered by this methodology are simple procedure, mild reaction condition, cleaner reaction and excellent yields of products. Additionally, L-proline can be recycled at least four times without significant loss of activity, which makes present protocol more convenient and environmentally benign. The investigation of antibacterial screening revealed that the sample compounds show varying degree of activity against all the tested micro-organism. Among all 3d

displayed very good activity. From antifungal activity results 3a-3f compound show good activity against all the fungal strains.

References:

1. a) Agarwal S.; Cammerer S.; Filali S.; Frohner W., J. Curr. Org. Chem., 2005, 9, 1601. B) Gonzalez J. F.; Ortin I.; Cuesta E. de la; Menendez J. C., Chem. Soc. Rev., 2012, 41, 6902.
2. Brown E.; Ring Nitrogen and Key Biomolecules. Kluwer Academic Press: Dordrecht, 1998.
3. Shirota Y.; J. Mater. Chem., 2000, 10, 1.
4. Jin Z.; Nat. Prod. Rep., 2003, 20, 584.
5. a) Pace A.; Pierro P., Org. Biomol. Chem., 2009, 7, 4337. B) Bostrom J.; Honger A.; Llinas A.; Wellner E.; Plowright A. T., J. Med. Chem., 2012, 55, 1817.
6. a) Kiselyov A. S., Eur. J. Med. Chem., 2010, 45, 1683. B) Kuznetsuv A.S., Eur. J. Med. Chem., 2007, 42, 893. C) Tully W. R.; Gardner C. R.; Gillespie R. J.; Westwood R., J. Med. Chem., 1991, 34, 2060.
7. a) James N. D.; Growcott J. W.; Drug Future, 2009, 34, 624. B) Tomkinson H.; Kemp J.; Oliver S.; Swaisland H.; Tadoada M.; Morris T., Clin. Pharmacol., 2011, 11, 3. C) Ogata M.; Atobe H.; Kushida H.; Yamamoto H., J. Antibiot., 1971, 24, 443.
8. Dobrota C.; Paraschivescu C. C.; Dumitru I.; Matache M.; Baciu I.;Ruta L. L.,Tetrahedron Lett., 2009, 50, 1886.
9. Shang Z.;Synth. Commun., 2006, 36, 2927.
10. Shang Z.; ReinerJ. J.; Chang, Zhao K., Tetrahedron Lett., 2005, 46, 2701.
11. Rostamizadeh S.; HousainiS.A.G.,Tetrahedron Lett., 2004, 34, 8753.
12. Saikahi H.; Shimojo N.; Uehara Y., Chem. Pharm. Bull., 1972, 20,1663.
13. Dabiri M.; Salehi P.; Baghbanzadeh M.; Bahramnejad M., Tetrahedron Lett., 2006, 47, 6983.
14. Yu W.; Huang G.; Zhang Y.; Liu H.; Dong L.; Yu X.; Li Y., J. Chang, J. Org. Chem., 2013, 78, 10337.

15. Tandon V. K.; Chhor R. B., Synth. Commun., 2001, 31, 1727.

Graphical abstract:

A series of 2,5-disubstituted-1,3,4-oxadiazole and its derivatives were synthesized. The oxadiazole derivatives were synthesized by the reaction of aromatic aldehydes and acyl hydrazides in the presence of L-proline.