ISSN(e): 2321-7545 Website: www.ijsae.in
International Journal of Scientific Research And Education
Volume||08||Issue||01||January-2020||Pages-8280-8283||ISSN(e):2321-7545
Website: http://jsae.in

Synthesis of Substituted 5-arylisoxazole derivatives in solvent free condition using ultrasontcation technique

Authors
Rajiv V Khobare[1], Ramkrushna P Pawar[2] , Khandu D Warad[1] , Amit P Tayde[3] , Chandrakant B. Mane[3]
[1]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India
[2]Department of Chemistry, Govt. Vidarbha Institute of Science and Humanities, Amravati-444604, India
[3]Shri Vijaysinha Yadav Arts and Science College, Pethvadgoan, Dist Kolhapur

ABSTRACT:
The present work is mainly designed to synthesize A series of 5-arylisoxazole derivatives were synthesized via the reaction of 3-(dimethyl-amino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in aqueous media without using any catalyst using ultrasound technique. The synthesized derivatives were subjected to antibacterial activity. All compounds showed good antibacterial activity. The salient features of this method include simple procedure, mild conditions, no waste produced (only by-product being water), easy purification, moderate to good yields of products and high generality.

Keywords: 5-arylisoxazole, antibacterial activity, ultrasound technique

INTRODUCTION

Heterocyclic compounds are of very much interest in our daily life.[1] Heterocyclic compounds have one or more heteroatoms in their structure having a wide range of application. They are predominantly used as pharmaceuticals, agrochemicals, and veterinary products. They also find applications as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, dyestuff. They are used as vehicles in the synthesis of other organic compounds.Some of the natural products e.g. antibiotics such as penicillin's, cephalosporin, alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moiety. More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery, and application is taking place is crossed by heterocyclic compounds. Heterocycles have shown considerable biological actions such as antibiotic[2], antifungal[3], anti-inflammatory[4], antiviral[5], anticancer[6], anticonvulsant[7], anthelmintic[8], antihistamine[9], antidepressant activities[10].

Out of several heterocycles one of the most interesting heterocyclic rings is an isoxazole that is a five membered ring containing oxygen and nitrogen atoms. Recent literature explains a broad spectrum of biological activities of isoxazole derivatives like anti-bacterial[11], antiviral, anti-cancer, immunomodulatory, anti-inflammatory, anti-Alzheimer, anti-platelet, anti-thrombotic anticonvulsant, analgesic and anti-diabetic activity.[12]

There are many reports for synthesis of isoxazole by conventional methods. The limitations of these methods includes that these methods requires strong acid, high temperature, and sometimes photoirradiation conditions, precious metal salts and oxidants[13]. Green chemistry is involving utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in synthesis chemical products is an important ecofriendly solution to above problem.

In the present research we have focused on a synthesis variety Synthesis of Substituted 5-arylisoxazole derivatives in solvent free condition using ultrasontcation technique.

.

MATERIAL AND METHOD

All reagents and chemicals were purchased from SD Fine or spectrochem chemical company, Mumbai, India. All reagents and chemicals were of analytical grade and used without further purification. Sonication was performed in ultrasonic cleaner with a frequency of 25 KHz and nominal power 250 W. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General procedure for the synthesis of substituted isoxazole

3-(Dimethylamino)-1-arylprop-2-en-1-one 1 (1 nmol), hydroxylamine hydrochloride 2 (1 nmol) and water (5 mL) were added to a 25-mL round-bottom flask. The mixture was then stirred at 50 °C for 2 h. After completion of the reaction, the mixture was then cooled to room temperature. The precipitate was collected by suction filtration to give products 3 without further purification.

The *in vitro* Antibacterial activity

The *in vitro* Antibacterial activity of compounds **5a-5e** were determined by agar cup plate method, the results of which are summarized in table belwo. The Antibacterial data clearly indicated that the diethylamino and bromo substituents of isoxazole ring were by far the most active substitutents. The other compounds generally confered week Antibacterial activity. The compounds **5b**, **5c** showed significant activity against *S. aureus* and *Pseudomonas aeruginosa*; however, the entire tested compounds were found to be less active as antibacterial in comparison to ciprofloxacin.

RESULTS

In present reaction an equivalent mixture of an 3-(dimethylamino)-1-arylprop-2-en-1-one derivative and hydroxylamine hydrochloride was stirred at 50°C in aqueous media to obtain 5-arylisoxazole derivatives.

The progress of the reaction was monitored by TLC. Structure of the synthesized compounds was established on the basis of physicochemical, elemental analysis and spectral data (IR, 1HNMR and Mass)..

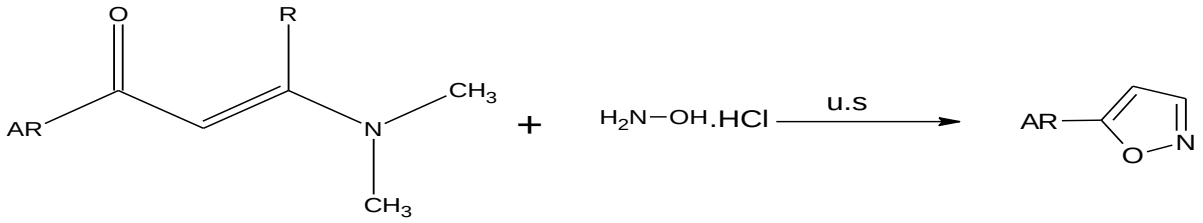

Fig 1: General scheme for synthesis of isoxazole

Table1: synthesis of various 5- aryl Isoxazole derivatives

Serial no	Product no	Product name	Melting Point ^{0}C	Reaction Time in min	%yield
1.	5a	5-(4-Chlorophenyl)isoxazole	84–86	18	86
2.	5b	5-(4-Methoxyphenyl)isoxazole	92–94	20	91
3.	5c	5-(4-Bromophenyl)isoxazole	81-83	19	80
4.	5d	5-(Naphthalen-1-yl)isoxazole	94-95	17	82
5.	5e	*3-Methyl-5-phenylisoxazole*	68-70	21	90

Representative spectra for 5-(4-Chlorophenyl)isoxazole

IR (KBr) *v*: 1601, 1447, 1264, 1128, 1109, 1088, 802 cm^{-1}; 1H-NMR (400 MHz, CDCl3) δ (ppm) 6.52 (d, *J* = 2.0 Hz, 1H, C4-H), 7.45 (d, *J* = 8.4 Hz, 2H, ArH), 7.73 (d, *J* = 8.4 Hz, 2H, ArH), 8.30 (d, *J* = 2.0 Hz, 1H, C3-H); $_{13}$C-NMR (75 MHz, CDCl3) δ (ppm) 98.9, 125.6, 127.0, 129.2, 136.1, 150.8, 168.1; HRMS calcd. for C9H7ClNO [M+H]+: 180.0216; found: 180.0215.

Table 2: Elemental analysis of 5-(4-Chlorophenyl)isoxazole

Serial no	**Element**	**Calculated %**	**Found %**
1.	Carbon	60.19	60.17
2.	Hydrogen	3.31	3.33
3.	chlorine	15.74	5.73
4.	Nitrogen	7.80	7.81
5.	Oxygen	8.91	8.91

The *in vitro* Antibacterial activity of compounds **5a-5e** were determined by agar cup plate method, the results of which are summarized in table belwo. The Antibacterial data clearly indicated that the diethylamino and bromo substituents of isoxazole ring were by far the most active substitutents. The other compounds generally confered week Antibacterial activity. The compounds **5b**, **5c** showed significant activity against *S. aureus* and *Pseudomonas aeruginosa*; however, the entire tested compounds were found to be less active as antibacterial in comparison to ciprofloxacin.

Serial no	Compound no	Zone of Inhibition *Pseudomonas aeruginosa*	Zone of Inhibition *Staphylococcus aureus*
1.	5a	19	21
2.	5b	21	23
3.	5c	25	27
4.	5d	19	18
5.	5e	18	16
6.	Ciprofloxacin	26	28

CONCLUSION

In conclusion, we have achieved isoxazole synthesis using green synthetic protocol under ultrasound irradiation technique. Further the compounds showed good antibacterial activity. Striking features of this method are short reaction time, easy work up procedure, water solvent, use of ultrasound waves, atom economy.

REFERENCES

(1) Arora, Pragi; Arora, Varun; Lamba, H. S.; Wadhwa, D. Importance of Heterocyclic Chemistry: *Int. J. Pharm. Sci. Reserach* **2012**, *3* (09), 2947–2954. https://doi.org/10.13040/IJPSR.0975-8232.3(9).2947-54.

(2) El-Mawgoud, H. K. A. Synthesis, in-Vitro Cytotoxicity and Antimicrobial Evaluations of Some Novel Thiazole Based Heterocycles. *Chem. Pharm. Bull. (Tokyo).* **2019**, *67* (12), 1314–1323. https://doi.org/10.1248/cpb.c19-00681.

(3) Zhang, M.-Z.; Jia, C.-Y.; Gu, Y.-C.; Mulholland, N.; Turner, S.; Beattie, D.; Zhang, W.-H.; Yang, G.-F.; Clough, J. Synthesis and Antifungal Activity of Novel Indole-Replaced Streptochlorin Analogues. *Eur. J. Med. Chem.* **2017**, *126*, 669–674. https://doi.org/10.1016/j.ejmech.2016.12.001.

(4) Abeed, A. A. O.; Jaleel, G. A. A.; Youssef, M. S. K. Novel Heterocyclic Hybrids Based on 2-Pyrazoline: Synthesis and Assessment of Anti-Inflammatory and Analgesic Activities. *Curr. Org. Synth.* **2019**, *16* (6), 921–930.

https://doi.org/10.2174/1570179416666190703115133.
(5) Dawood, K. M. An Update on Benzofuran Inhibitors: A Patent Review. *Expert Opin. Ther. Pat.* **2019**, *29* (11), 841–870. https://doi.org/10.1080/13543776.2019.1673727.
(6) Kale, M.; Sonwane, G.; Nawale, R.; Mourya, V. Molecular Modeling Studies on Some Important Anticancer Heterocycles: An Overview. *Curr. Comput. Aided. Drug Des.* **2018**, *14* (3), 178–190. https://doi.org/10.2174/1573409914666180321105745.
(7) Zinad, D. S.; Mahal, A.; Mohapatra, R. K.; Sarangi, A. K.; Pratama, M. R. F. Medicinal Chemistry of Oxazines as Promising Agents in Drug Discovery. *Chem. Biol. Drug Des.* **2020**, *95* (1), 16–47. https://doi.org/10.1111/cbdd.13633.
(8) Vairoletti, F.; Medeiros, A.; Fontan, P.; Melendrez, J.; Tabarez, C.; Salinas, G.; Franco, J.; Comini, M. A.; Saldana, J.; Jancik, V.; et al. Synthesis of Bicyclic 1,4-Thiazepines as Novel Anti-Trypanosoma Brucei Brucei Agents. *Medchemcomm* **2019**, *10* (8), 1481–1487. https://doi.org/10.1039/c9md00064j.
(9) Cao, X.; Zhang, Y.; Chen, Y.; Qiu, Y.; Yu, M.; Xu, X.; Liu, X.; Liu, B.-F.; Zhang, L.; Zhang, G. Synthesis and Biological Evaluation of Fused Tricyclic Heterocycle Piperazine (Piperidine) Derivatives As Potential Multireceptor Atypical Antipsychotics. *J. Med. Chem.* **2018**, *61* (22), 10017–10039. https://doi.org/10.1021/acs.jmedchem.8b01096.
(10) Garg, V.; Maurya, R. K.; Thanikachalam, P. V.; Bansal, G.; Monga, V. An Insight into the Medicinal Perspective of Synthetic Analogs of Indole: A Review. *Eur. J. Med. Chem.* **2019**, *180*, 562–612. https://doi.org/10.1016/j.ejmech.2019.07.019.
(11) Bi, F.; Song, D.; Zhang, N.; Liu, Z.; Gu, X.; Hu, C.; Cai, X.; Venter, H.; Ma, S. Design, Synthesis and Structure-Based Optimization of Novel Isoxazole-Containing Benzamide Derivatives as FtsZ Modulators. *Eur. J. Med. Chem.* **2018**, *159*, 90–103. https://doi.org/10.1016/j.ejmech.2018.09.053.
(12) Sysak, A.; Obminska-Mrukowicz, B. Isoxazole Ring as a Useful Scaffold in a Search for New Therapeutic Agents. *Eur. J. Med. Chem.* **2017**, *137*, 292–309. https://doi.org/10.1016/j.ejmech.2017.06.002.
(13) Drisko, C. R.; Griffin, S. A.; Huang, K. S. Solid-Phase Synthesis of [4.4] Spirocyclic Oximes. *J. Vis. Exp.* **2019**, No. 144. https://doi.org/10.3791/58508.