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AN EFFICIENT ULTRASOUND ASSISTED ASPARTIC ACID CATALYZED MULTICOMPONENT SYNTHESIS OF ISOXAZOLE-5(4H)-ONES

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ABSTRACT

A green and efficient protocol was developed for the multicomponenet synthesis of isoxazoles via the Ethanol:water mediated multicomponent reaction of aromatic aldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride in ultrasonic conditions catalyzed by aspartic acid at ambient conditions. It is noteworthy that the aspartic acid promoted one-pot three-component process under ultrasonic conditions was observed to be very good and satisfactory.

KEYWORD:- Isoxazole, Aspartic acid, Ultrasound.

INTRODUCTION

Isoxazoles are aromatic heterocycles with five members that have nitrogen and oxygen atoms next to each other. Many naturally occurring substances and physiologically active molecules have the isoxazole ring structure.[1] Numerous biological activities, including anti-inflammatory, antifungal, antiplatelet, anti-Alzheimer, anti-HIVand analgesic properties, are exhibited by isoxazole derivatives.[2-5] Multicomponent reactions are processes that create a desired single product using readily available or commercially available starting components. There are far fewer processes involved in obtaining the target chemicals in a single pot. In order to produce heterocyclic compounds, multicomponent reactions have drawn a lot of attention in fields of combinatorial chemistry and medicinal chemistry.[6-8] In both academia research and industry, the use of ultrasonic irradiation to accelerate organic processes has long been recognized. Thus ultrasound irradiation has been utilized in organic chemistry, medicinal chemistry and material sciences. Ultrasound's chemical and physical impacts are caused by acoustic cavitations, which include the creation, expansion, and implosive collapse of bubbles in a liquid.[9-11] A number of catalysts have been used in one-pot MCRs of benzaldehyde, ethyl acetoacetate, and hydroxylamine for the synthesis of isoxazole scaffold including potassium hydrogen phthalate,[12] N-bromosuccinimide,[13] pyridinium p-toluenesulfonate,[14] 1 4-aminobenzene-1-sulfonic acid,[15] iodine,[16] pyridine[17] phosphotungstic acid[18] etc.

However lower yield, utilization of harsh conditions, the use of hazardous chemicals and solvents, and the need for longer reaction times are some of the drawbacks of the reported synthetic procedures. Therefore, there is a great need to develop efficient and environmentally friendly processes for the synthesis of Isoxazole-5(4H)-ones. So in this protocol and in continuation of our previous works towards development of new convenient protocols,[19-25] we present here aspartic acid catalyzed, one-pot, three-component method for the quick synthesis of substituted Isoxazole-5(4H)-one scaffolds using a aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride in EtOH: water as a solvent under ultrasonic conditions at room temprature.

RESULTS AND DISCUSSION

To produce the desired aryl-3-methylisoxazol-5(4H)-ones, a one-pot multicomponent reaction was utilized in an aqueous ethanol medium with suitable substrates catalyzed by aspartic acid in ultrasonic conditions (Figure 1).

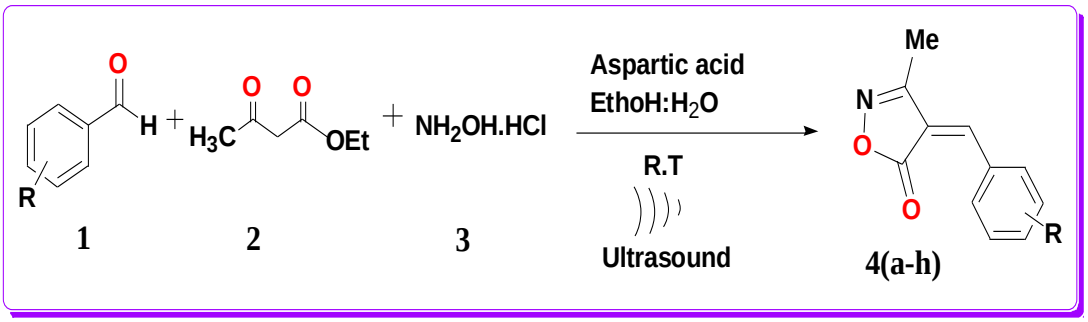
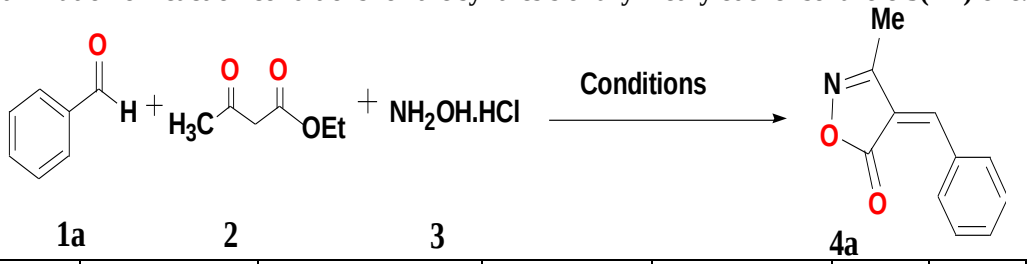


Figure 1: An Ultrasound assisted Aspartic acid catalyzed synthesis of arylmethyledene-isoxazole-5(4H)-ones.

Initially, a model reaction was carried out with benzaldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride. A variety of parameters were examined, including various solvents, catalyst loading, conventional and ultrasonic conditions and the reaction progress was monitored by TLC.

Our focus of was to incorporate an efficient, green and more convenient methodology for the multicomonent synthesis of these isoxazoles. When the reaction was carried out in ethanol alone using aspartic acid (20 mol%) as a catalyst at room temperature gave 85% of yield (Table 1, entry1). When water alone was used as a solvent keeping other parameters constant poor yield of the corresponding product was obtained (Table 2, entry 2). Similar good results were obtained when EtOH: H_2O (1:1) used instead of ethanol alone (Table 1, entry 3). In order to improve the results, instead of conventional procedure, ultrasound assisted protocol was employed. This showed a noticeable impact on the yield and Improvement in the reaction profile in terms of reaction time (40 min) and yield (92%) was observed at ultrasound conditions (Table 1, entry 4). For optimization of catalyst loading, performing the same reaction in the presence of 10 mol% aspartic acid catalysts in an aqueous ethanol medium at R.T. and under ultrasound irridation led to the formation of less amount of 4a after 2 hr (Table 1, entry 5). Whereas increasing the aspartic acid concentration to 30 mol% did not offers noticeable change in the results as compared to using 20 mol% of the catalyst (Table 1, entry 6). Therefore it was conclude that 20 mol% of aspartic acid catalyst was sufficient to obtain the desired product 4a in 92 % yield after 40 min stirring at room temperature and under ultrasound conditions (Table 1, entry 4). No improvement was observed in the reaction profile when different solvents were utilized in the ultrasonic protocol such as acetonitrile and methanol (Table 2, entries 7, 8). Thus, the optimum reaction condition for the reaction was noted, when the benzaldehyde (1a), hydroxylamine hydrochloride (2) and ethyl acetoacetate (3) was sonicated in EtOH:H2O (1:1) at room temperature in the presence of 20 mol% aspartic acid catalyst which afforded desired isoxazole derivative (4a) in 92 % yield in 40 min (Table 2, entry 4).

Table 1: Optimization of reaction conditions for the synthesis of arylmethyledene-isoxazole-5(4H)-one.



Entry	Condition	Solvents [a]	Aspartic Acid(mol%)	Temperature (^oC)	Time (min)	Yield (%)[b]
1	Conventional	EtOH	20	R.T	75	85
2	Conventional	H_2O	20	RT	120	62
3	Conventional	EtOH:H_2O (1:1)	20	R.T	75	85
4	Ultrasound	EtOH:H_2O (1:1)	20	RT	40	92
5	Ultrasound	EtOH:H_2O (1:1)	10	RT	120	60
6	Ultrasound	EtOH:H_2O (1:1)	30	RT	40	92
7	Ultrasound	Acetonitrile	20	RT	120	60
8	Ultrasound	MeOH	20	RT	120	65

[a] 5mL, [b]Isolated yields.

To test the generality of the developed protocol different derivatives are prepared, as shown in Table 2, and it was found that this new procedure works with a variety of substrates present on benzene ring of aldehydes. The

reaction was carried out with six different types of substituted aromatic aldehydes and it was observed that yields are consistently very good regardless of the substituent's type and position (Table 2, entries 1-6).

Table 2: An Ultrasound assisted Aspartic acid catalyzed synthesis of arylmethyledene-isoxazole-5(4H)-ones.

Entry	R	P	Yield (%)[a]	Time (min)	M. p (°C)	
					Observed	Literature[12-18]
1	H	4a	92	40	140-142	141-143
2	4-CH_3O	4b	91	50	176-178	175-177
3	4-CH_3	4c	90	50	132-134	132-134
4	4-NO_2	4d	88	60	181-183	183-184
5	4-Cl	4e	86	60	122-124	128-130
6	4-OH	4f	89	55	222-224	213-215
7	2-OH	4g	87	45	192-194	197-199
8	4-NO_2	4h	86	60	138-140	---------

[a]Isolated yields..

CONCLUSION

We have developed a new protocol for the synthesis of different substituted isoxazole derivatives (4a-4g) using a one-pot three-component reaction between substituted aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride under ultrasound irradiation in the presence of aspartic acid as an efficient organo-catalyst in aqueous ethanol medium under ultrasonic irradiation. The current methodology offers several advantages, including green ultrasonic conditions, the use of a safe and easily available aspartic acid organo-catalyst, ethanol: water as a green medium, rapid reaction completion, and maximum yields.

EXPERIMENTAL SECTION

MATERIAL AND METHODS

Chemicals were purchased from SD Fine Chemical Companies. The physical properties of the synthesized derivatives were confirmed by comparing the physical data with those described in the literature. A Bruker Advance NEO spectrometer was used to record NMR spectra, and mass spectra were recorded on the Waters GC-MS spectrophotometer. Silica gel TLC plates were used to monitor the reactions and the purity of the products."

Typical Procedure for the synthesis of arylmethylidene-isoxazol-5(4H)-ones (4a-h)

In a 25mL RBF an aromatic aldehyde (1 mmol) was added to a well stirred mixture of ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and aspartic acid (20 mol%) in EtOH:H_2O (5 mL, 1:1), and the mixture was agitated at room temperature in the Ultrasound irradiated bath for the required amount of time as indicated by thin layer chromatography (Ethyl acetate:Hexane, 2:8). After reaction completion, 5 mL of water was added, and the resulting solid crude precipitate was filtered. To obtain the pure product, the crude product was recrystallized from a mixture of EtOH-H_2O (4:1).

Spectral data

3-Methyl-4-(4-methoxyphenyl)methylene-isoxazole-5(4H)-one (4a): M.p. 175-178 °C; ^{1}H NMR (500 MHz, $CDCL_3$) δ(ppm): 2.27 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 7.01 (2H, d, J = 8.9 Hz, HAr), 7.34 (1H, s, =CH), 8.44 (2H, d, J = 8.9 Hz, HAr); ^{13}C NMR(125 MHz, $CDCL_3$) δ(ppm): 11.63, 55.71, 114.66, 116.37, 125.83, 136.96, 149.32, 161.27, 164.61, 168.77, Mass, m/z: 218.08 [M+1].

REFERENCES

1. Barmade MA, Murumkar PR, Sharma MK, Yadav MR Medicinal chemistry perspective of fused isoxazole derivatives. Curr Top Med Chem, 2016; 16: 2863–2883.
2. Jin RY, Sun XH, Liu YF, Long W, Chen B, Shen SQ, Ma HX Synthesis, crystal structure, biological activity and theoretical calculations of novel isoxazole derivatives. Spectrochim Acta Part A, 2016; 152: 226–232.
3. Gutierrez M, Amigo J, Fuentes E, Palomo I, Astudillo L Synthetic isoxazole as antiplatelet agent. Platelets, 2014; 25: 234–238.
4. Filali I, Romdhane A, Znati M, Jannet HB, Bouajila J Synthesis of new harmine isoxazoles and evaluation of their potential anti-Alzheimer, anti-infammatory, and anticancer activities. Med Chem, 2016; 12: 184–190.
5. Ali MA, Ismail R, Choon TS, Yoon YK, Wei AC, Pandian S, Samy JG, De Clercq E, Pannecouque C Synthesis and anti-HIV activity of novel 3-substituted phenyl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c] isoxazole analogues. Acta Pol Pharm, 2011; 68: 343-348.
6. Armstrong, R.W.; Combs, A.P.; Tempest, P.A.; Brown, S.D.; Keating, T.A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. Acc. Chem. Res, 1996; 29: 123-131.
7. Pagadala, R.; Kasi, V.; Shabalala, N.G.; Jonnalagadda, S.B. Ultrasound-assisted multicomponent synthesis of heterocycles in water-A review. Arab. J. Chem, 2022; 15: 103544-103564.
8. Nandi, S.; Jamatia, R.; Sarkar, R.; Sarkar, F.K.; Alam, S.; Pal, A.K. One-Pot Multicomponent Reaction: A Highly Versatile Strategy for the Construction of Valuable Nitrogen-Containing

Heterocycles. Chemistry Select, 2022; 7: e202201901.
9. Ray S, Manna P and Mukhopadhyay C, Simultaneous sonication assistance for the synthesis of pyrroloacridinones and its efficient catalyst HBF4 supported on uniform spherical silica nanoparticles Ultrason. Sonochem, 2015; 22: 22.
10. Mason T J Ultrasound in synthetic organic chemistry Chem. Soc. Rev, 1997; 26: 44367.
11. Wang S F, Guo C L, Cui K K, Zhu Y T, Ding Z X, Zou X Y and Li Y H, Lactic acid as an invaluable green solvent for ultrasound-assisted scalable synthesis of pyrrole derivatives Ultrason. Sonochem, 2015; 26: 81.
12. Maleki B, Baghayeri M, Abadi S A J, Tayebee R and Khojastehnezhad A, Ultrasound promoted facile one pot synthesis of highly substituted pyran derivatives catalyzed by silica-coated magnetic NiFe2O4 nanoparticle- supported H14[NaP5W30O110] under mild conditions RSC Adv, 2016; 6: 96644
13. Kiyani H and Ghorbani F, Efficient tandem synthesis of a variety of pyran-annulated heterocycles, 3,4-disubstituted isoxazol-5(4H)-ones, and a, b-unsaturated nitriles catalyzed by potassium hydrogen phthalate in water Res. Chem. Intermed, 2015; 41: 7847.
14. Kiyani H, Kanaani A, Ajloo D, Ghorbani F and Vakili M N-Bromosuccinimide (NBS)-promoted, three component synthesis of a, b-unsaturated isoxazol- 5(4H)-ones, and spectroscopic investigation and computational study of 3-methyl-4-(thiophen-2-ylmethylene) isoxazol-5(4H)-one Res. Chem. Intermed, 2015; 41: 7739.
15. Laroum R and Debache, A New eco-friendly procedure for the synthesis of 4-arylmethylene-isoxazol- 5(4H)-ones catalyzed by pyridinium p-toluene sulfonate (PPTS) in aqueous medium Synth. Commun, 2018; 48: 1876.
16. Kiyani H and Mosallanezhad A Sulfanilic acidcatalyzed synthesis of 4-arylidene-3-substituted isoxazole- 5(4H)-ones Curr. Org. Synth, 2018; 15: 5-715.
17. Nakkalwar S L, Patwari S B, Patel M M and Jadhav V B, Iodine catalyzed highly efficient one pot three component synthesis of 4-arylidene-3-methylisoxazol- 5(4H)-one in aqueous medium Curr. Green Chem, 2018; 5: 2-122.
18. Ablajan K and Xiamuxi H, Efficient one-pot synthesis of b-unsaturated isoxazol-5-ones and pyrazol- 5-ones under ultrasonic irradiation Synth. Commun, 2012; 42: 1128.
19. Fozooni S, Hosseinzadeh N G, Hamidian H and Akhgar M R Nano Fe2O3, clinoptilolite and H3PW12O40 as efficient catalysts for solvent-free synthesis of 5(4H)-isoxazolone under microwave irradiation conditions J. Braz. Chem. Soc, 2013; 24: 1649.
20. Abdul Ahad and Maqdoom Farooqui, "Choline chloride and urea based deep eutectic solvent promoted synthesis of arylmethylidene-isoxazol-5(4H)-ones", International Journal of ChemTech Research, 2017; 10(6): 269-273.
21. Abdul Ahad and Maqdoom Farooqui, Chemical Science Transactions, "Glycine catalyzed synthesis of 3-Indole derivatives mediated by PEG-400 in water", Chemical Science Transactions, 2016; 5(1): 202-206.
22. Abdul Ahad and Maqdoom Farooqui, An efficient synthesis of 3-amino alkylated indole Via A Mannich-Type reaction catalyzed by SiO2-I, Heterocyclic Letters, 2017; 7(4): 953-958.
23. Abdul Ahad and Maqdoom Farooqui, "Pot, atom and step economic (PASE) synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines in aqueous PEG-400 promoted by sodium benzoate, International Journal of Chemical Sciences, 2016; 14(3): 1789-1796.
24. Abdul Ahad and Maqdoom Farooqui, Organocatalyzed domino reactions: Diversity oriented synthesis of pyran-annulated scaffolds using in situ-developed benzylidenemalononitriles, Research on Chemical intermediates, 43(4): 2445-2455.
25. Abdul Ahad and Maqdoom Farooqui, Recyclable Amberlite IR-120 catalyzed synthesis of 3-substituted indoles", Chemistry & Biology Interface, 2015; 5(5).
26. Abdul Ahad and Maqdoom Farooqui, Hydroquinolines via the Hantzsch reaction promoted by SiO_2-I, Organic Preparations and Procedures International-Taylor & Francis, 2016; 48, 4: 371-376.