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Solid fly-ash: H_2SO_4 is an efficient catalyst for cyclization of α,β-unsaturated ketones: Solvent-free synthesis of some oxazine amine derivatives

G. Thirunarayanan[1] and K. G. Sekar[2]*

[1]Department of Chemistry, Annamalai University, Annamalainagar, India
[2]Department of Chemistry, National College, Tiruchirappalli, India

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ABSTRACT

Attempts to synthesis some aryl oxazine amines [5,6-dihydro-4-aryl-6-(substituted phenyl)-2H-1,3-oxazin-2-amines] by fly-ash:H_2SO_4 catalyzed solvent-free cyclization of aryl chalcones and urea under microwave irradiation. The yield of the oxazines were more than 85%. These oxazine imines were characterized by their physical constants and spectroscopic data.

Key words: Oxazine amines, α,β-unsaturated ketones, fly-ash:H_2SO_4, Environmentally benign reaction

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INTRODUCTION

The six membered heterocyclic compounds possess one oxygen and one nitrogen atom are known as oxazines[1,2]. These oxazine molecules exists many isomeric structures such as 1, 2 or 1, 3 or 1, 4 oxazines types[3] depend upon the relative position of these tow atoms and the double bond.These oxazines were medicinally important due to the presence of oxygen, nitrogen heteroatoms along with a double bonds in their structural moieties[4]. The important medicinal activities of these oxazine derivatives are anti-bacterial[4-6], anti-fungal[4-6], anti-plasmodial[7], anti-cancer[8], anti-depressants[9], cytotoxicity[10], anti-osteoplastic[11], anti-tumour[12], anti-oxidant[13], anti-tuberculosis[14], anti-neoplastic[15], antagonists[16], anti-inflammatory[17], anti-infectants[18], IKB kinasebeta[19] and PTP-1B inhibition[20]. These oxazine derivatives were applied for improving the super resolution microscope[21], synthesis of eosinophils[22], identification and separation of neutrophils[23]. Many oxazine derivatives were used as a dyes[24]. Numerous solvent assisted and solvent-free synthetic methods were available for synthesis of oxazinederivatives[25]. Now-a-days scientists, organic chemists are interested for solvent-free synthesis[5, 26-28,29,30,31]. Some reactions such as hetero Diels-alder reaction[4], ring closure[32], Betti base induced condensation[33], Mannich type condensation-cyclization[5] and cyclization of chalcones[6] were used for synthesis of oxazine derivatives. Verma et. al.[26] have synthesised some benzoxazine/oxazine fused isoquinolines and naphthyridines by solvent-free method. Elarfi and Al-difar[6] have synthesised some 1, 3-oxazine derivatives by solvent-assisted method from chalacones and urea. More than 75% yield of dihydro-^{2}H-benzo- and naphtho-1,3-oxazine derivatives were prepared by Mathew et al.[5] using eco-friendly method. Efficient synthesis of some 1, 3-oxazine-4-thiones were synthesised by N-methylimidazole promoted solvent-free conditions. Sapkal et al., have studied the role of ammonium acetate for solvent-free synthesis of 1,3-disubstituted-2,3-dihydro-^{1}H-naphthyl oxazines[28]. Within the above view, there is no information available in the literature for the solvent-free synthesis of 2-naphthyl based oxazine 2-amine derivatives. Therefore the authors have taken effort to synthesize some 2-naphthyl based oxazine amines and characterized by their analytical and spectral data.

MATERIALS AND METHODS

General

All chemicals were used in this present study were purchased from Sigma-Aldrich and Merck Chemical companies. Mettler FP51 melting point apparatus was used for determining the melting point of all synthesized oxazines in open glass capillaries and are uncorrected. The AVATAR-300 Fourier transform spectrophotometer was used for recording infrared spectra (KBr, 4000-400 cm^{-1}) of all oxazines in KBr disc. The Bruker AV400 series type NMR spectrometer was utilized for recording NMR spectra of all oxazines, operating at 400MHz for ^{1}H and100 MHz for ^{13}C spectra in $CDCl_3$ solvent using TMS as internal standard. Mass spectra of all synthesised oxazines were recorded on SHIMADZU mass spectrometer using chemical ionization technique.

Preparation of fly-ash:H_2SO_4 catalyst

The fly-ash:H_2SO_4 catalyst and the aryl chalcones were prepared according to literature procedure[34].

Synthesis of 4-(aryl)-5,6-dihydro-6-(substituted phenyl)-4H-1,3-oxazine-2-amines.

Equi-molar quantities of chalcones(2 mmol), urea(2mmol) and 0.5 g of fly-ash:H_2SO_4 were taken in a 50 mL beaker, closed with the lid. This mixture was subjected to microwave irradiation for 2-4 m at 650W (Scheme 1) (Samsung, Microwave Oven, 100-700W). After completion of the reaction, dichloromethane (10 mL) was added, followed by simple filtration. The solution was concentrated and purified by re-crystallization. The synthesized oxazines were characterized by their physical constants, IR, ^{1}H and ^{13}C NMR and Mass spectral data. Analytical and Mass spectral data are presented in Table 1.

Scheme 1. Synthesis of 4-aryl-5,6-dihydro-6-(substituted phenyl)-4H-1,3-oxazine-2-amines by fly-ash:H_2SO_4 catalyzed cyclization of aryl chalcones and urea under microwave irradiation

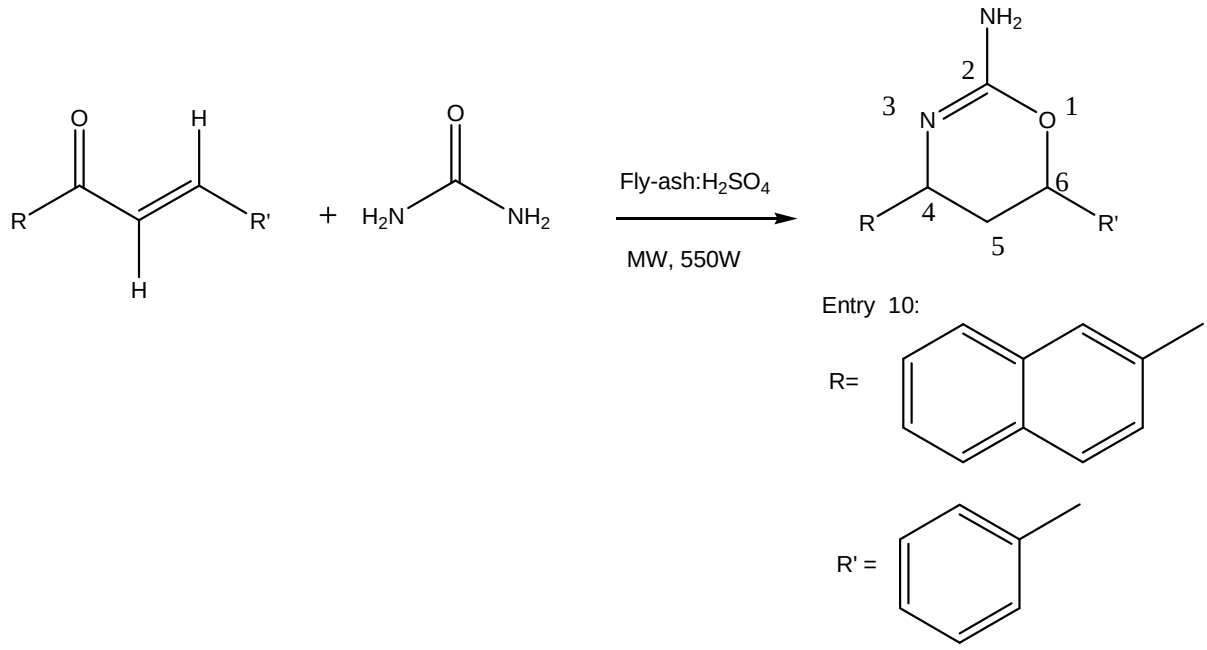
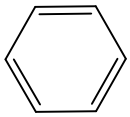
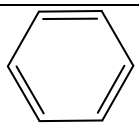
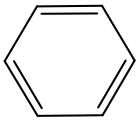
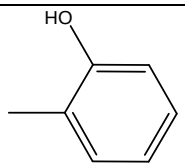
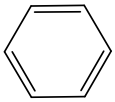
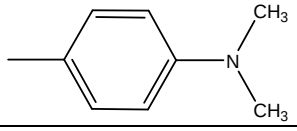
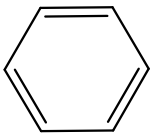
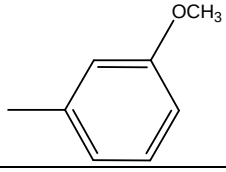
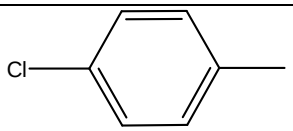
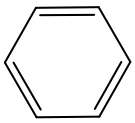
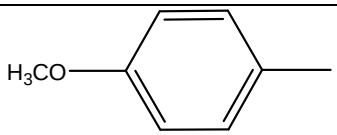
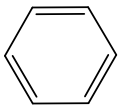
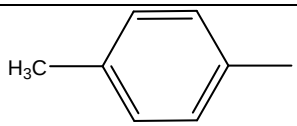
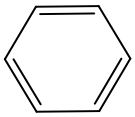
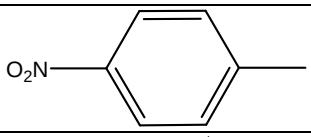
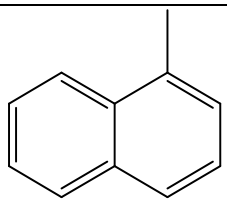
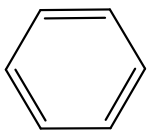
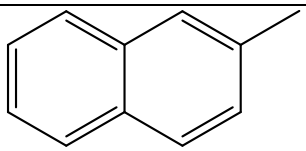
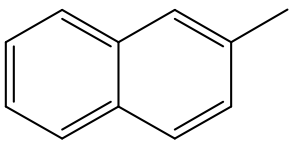
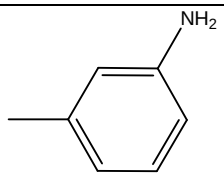
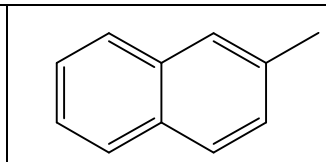
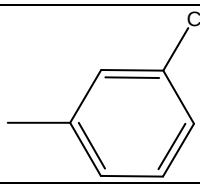
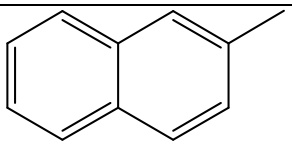
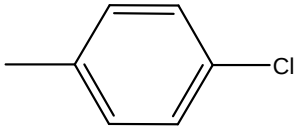
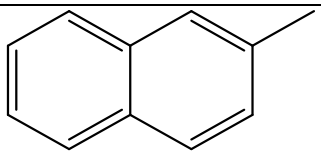
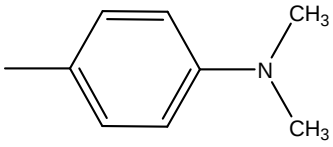
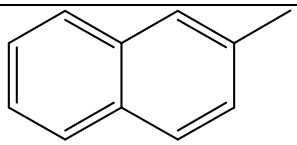
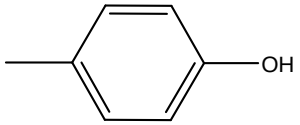
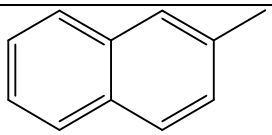
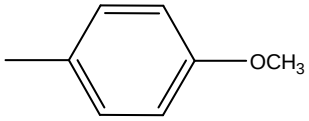
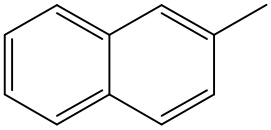
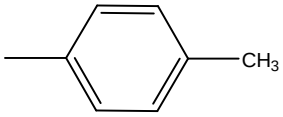
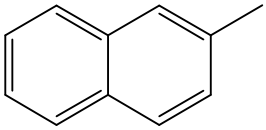
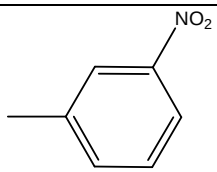
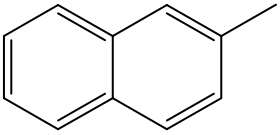
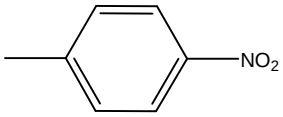


Table 1. Analytical, physical constants, yield and mass fragment of 4-aryl-5,6-dihydro-6(substituted phenyl)-4H-1,3-oxazine-2-amines

Entry	R	R′	M.W.	Yield (%)	m.p.(°C)	Mass (m/z)
1			252	88	134-136	252[M^+], 236, 175, 160, 84, 77, 43, 42, 16
2			268	85	144-145 (145-146)[23]	268[M^+], 252, 251, 236, 175, 160, 99, 93, 84, 77,43, 42, 16
3			295	87	65-66 (65-66)	295[M^+], 280, 265, 279, 251, 236, 175, 160, 118, 84, 77, 44, 43, 42, 30, 16, 15
4			282	89	122-123	282[M^+], 266, 251, 236, 205, 190, 175, 160, 107, 91, 84, 77, 43, 42, 31, 16
5			288	85	115-116	286[M^+], 288[M^{2+}], 270, 266, 251, 175, 160, 111, 107, 99, 84, 77, 43, 42, 35, 16
6			282	89	132-133	282[M^+], 266, 251, 256, 236, 205, 190, 175, 160, 107, 91, 84, 77, 43, 42, 31, 16
7			266	88	112-113	266[M^+], 251, 250, 175, 160, 91, 84, 77, 43, 42, 31, 16, 15
8			297	85	141-142	297[M^+], 281, 251, 175, 168, 160, 122, 84, 77, 45, 43, 42, 16
9			302	87	98-99	302[M^+], 286, 225, 210, 159, 127, 99, 84, 77, 52, 43, 42, 16
10			302	86	109-110	302[M^+], 286, 356, 225, 210, 175, 159, 127, 99, 91, 84, 77, 52, 43, 42, 16
11			355	88	116-117	355[M^+], 324, 263, 248, 190, 165, 99, 92, 77,58, 43, 42, 41,16,

12			375	85	121-122	375[M^+], 377[M^{2+}], 358, 339, 263, 248, 209, 175, 165, 118, 111, 84, 77, 58, 43, 35,16,
13			375	85	115-116	375[M^+], 377[M^{2+}], 358, 263, 248, 209, 175, 118, 84, 77, 58, 43, 42, 35,16,
14			383	87	131-132	383[M^+], 368, 353, 339, 263, 254, 165, 147, 106, 91, 77, 58, 44,43, 42, 16, 15
15			356	86	124-125	356[M^+], 340, 339, 263, 248, 165, 99,93, 84, 77, 58, 43, 42, 16,
16			370	91	112-113	370[M^+], 339, 354, 290, 263, 205, 165, 148, 107, 91, 77, 58, 43, 42, 31, 16
17			354	90	117-118	354[M^+], 339, 354, 291, 262, 205, 229,175 148, 107, 91, 77, 58, 43, 42, 31, 16
18			386	85	126-127	386[M^+], 339, 369, 327, 263, 248, 205, 165, 122, 84,77, 46, 43, 41, 16,
19			386	86	134-135	386[M^+], 339, 369, 327, 248, 205, 165, 84,77, 46, 43, 41, 16,

RESULTS AND DISCUSSION

In our organic chemistry research laboratory, the authorshave attempts to synthesize oxazine derivatives by cyclization of chalcones possess electron with-drawing as well as electron donating group as substituents, urea and in the presence of acidic catalyst fly-ash:H_2SO_4 using microwave irradiation. Hence the authors have synthesized some substituted 1,3-oxazine derivatives by the cyclization of 2 mmole of chalcone, 2 mmole of urea under microwave irradiation with 0.5g of fly-ash:H_2SO_4 catalyst at 550W for 4-6 minutes (Samsung Grill, GW73BD Microwave oven, 230V A/c, 50Hz, 2450Hz, 100-750W (IEC-705), (Scheme 1). During the course of this reaction fly-ash:H_2SO_4 catalyses cyclization between chalcones and urea followed by rearrangement gave the 1, 3-oxazine amines. The yields of the oxazine in this reaction are more than 80%. The chalcone containing electron donating substituent (OCH_3) gave higher yields than electron-withdrawing (halogens, NO_2) substituents. Further we have investigated this cyclization reaction with equimolar quantities of the styryl 2-naphthyl ketone (**entry 10**) and urea under the same condition as above. In this reaction the obtained yield was 90%. The effect of catalyst on this reaction was studied by varying the catalyst quantity from 0.1 g to 1 g. As the catalyst quantity is increased from 0.1 g to 1 g, the percentage of yield of product is increased from 84 to 90%. Further increase in the catalyst amount beyond 0.4 g, there is no significant increase in the percentage of the product. The effect of catalyst loading is shown in Fig. 1. The optimum quantity of catalyst loading was found to be 0.4 g. The results, analytical and mass spectral data are summarized in Table 1. The reusability of this catalyst was studied for the cyclization of styryl 2-naphthyl ketoneand urea (**entry 10**) is presented in Table 2. From the Table 2, first two runs gave 90% product. The third, fourth and fifth runs of reactions gave respectively the yields 89.5%, 89.5% and 89% of oxazines. There was no appreciable loss in its effect of catalytic activity observed up to fifth run.

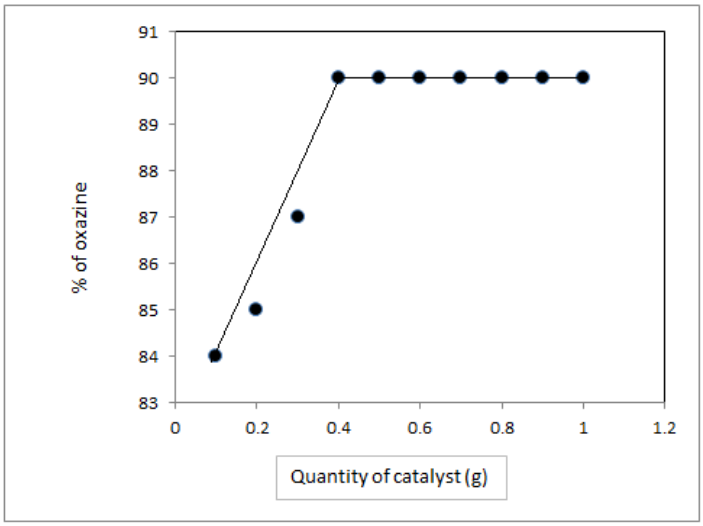


Figure 1.Effect of catalyst loading

Table 2.Reusability of fly-ash:H_2SO_4 catalyst on cyclization of styryl 1-naphthyl ketone (2 mmol) with urea (2 mmol) under microwave irradiation(entry 10)

Run	1	2	3	4	5
Yield	90	90	89.5	89.5	89

Table 3.The effect of solvents in conventional heating and without solvent in microwave irradiation on yield of oxazineamine (entry 10).

SOLVENTS													MW		
MeOH			EtOH			DCM			THF						
FA	SA	FASA	FA	SA	FASA	FA	SA	FASA	FA	SA	FAPA	FA	SA	FASA
66	24	75	65	26	81	64	20	85	60	20	80	69	38	90

MeOH=Methanol; EtOH=Ethanol; DCM= Dichloromethane; THF=Tetrahydrofuran; FA=fly-ash; SA=Sulphuric acid; FASA=fly-ash:H_2SO_4

Table 4. Infrared and NMR spectroscopic data of 4-aryl-5,6-dihydro-6(substituted phenyl)-4H-1,3-oxazine-2-amines

Entry	IR(ν, cm^{-1})				^{1}H(δ, ppm)							^{13}C(δ, ppm)	
	NH	C=N	C-O-C	Substt.	NH(*s*)	H_4(*dd*)	H_5(*dd*)	H_5(*dd*)	H_6(*dd*)		Substt.	C_2	C_4
1	3534	1598	1234	---	2.345	2.625	2.425	2.214	4.257	6.545-7.345	---	165.33	52.56
2	3564	1628	1245	3564 (OH)	2.295	2.598	2.465	2.201	4.351	6.289-7.258	---	164.82	51.36
3	3526	1614	1264	---	2.214	2.491	2.458	2.269	4.451	6.358-7.298	3.658 $N(CH_3)_2$	164.35	52.36
4	3514	1610	1236	1238 (OCH_3)	2.361	2.412	2.542	2.230	4.652	6.257-7.987	4.023 (OCH_3)	164.03	52.28
5	3536	1599	1265	---	2.173	2.918	2.350	2.113	4.714	7.174-7.291	---	164.17	52.07
	3525	1621	1218	1225 (OCH_3)	2.277	2.753	2.299	2.217	4.593	6781-7.352	3.997 (OCH_3)	163.21	52.19
7	3536	1593	1214	---	2.197	2.807	2.245	2.172	4.673	6.917-7.352	2.514 (CH_3)	164.44	52.84
8	3558	1624	1265	---	2.317	2.897	2.436	2.223	4.709	7.273-8.165	---	165.23	52.78
9	3523	1589	1212	---	2.295	2.384	2.201	2.236	4.652	6.259-7.962	---	164.99	51.36
10	3526	1598	1215	---	2.291	2.301	2.221	2.245	4.252	6.325-7.852	---	165.02	52.01
11	3548	1592	1210	3355 (NH_2)	2.112	2.253	2.215	2.321	4.667	6.514-7.921	4.886 (NH_2)	165.25	52.28
12	3545	1605	1215	---	2.225	2.219	2.265	2.025	4.632	6.725-7.787	---	164.25	52.65
13	3535	1589	1222	---	2.125	2.258	2.264	2.038	4.671	6.825-7.887	---	165.28	52.87
14	3552	1621	1214	---	2.091	2.224	2.318	2.187	4.752	6.622-7.974	3.725	164.57	52.38
15	3545	1596	1221	3545 (OH)	2.204	2.325	2.342	2.165	4.285	6.625-7.895	---	165.33	52.82
16	3532	1613	1215	1220 (OCH_3)	2.220	2.232	2.345	2.112	4.362	6.825-7.932	4.062 (OCH_3)	164.72	52.32
17	3535	1622	1221	---	2.212	2.229	2.262	2.119	4.482	6.281-7.835	2.620 (OCH_3)	164.47	52.51
18	3555	1625	1215	---	2.321	2.233	2.395	2.154	4.622	6.823-7.598	---	165.41	52.32
19	3555	1648	1217	---	2.182	2.212	2.324	2.028	4.635	6.521-7.995	---	165.32	52.85

Entry	$^{13}C(\delta, ppm)$			
	C_5	C_6	Ar-C	Substt.
1	47.33	65.90	125.36-142.25	---
2	47.98	66.25	126.25-139.38	---
3	47.01	65.98	122.68-139.25	44.38 $N(CH_3)_2$
4	48.74	65.39	121.36-141.25	62.38 (OCH_3)
5	47.95	67.03	126.43-139.40	---
6	47.94	66.79	114.54-137.36	56.78(OCH_3)
7	47.17	66.84	125.77-139.04	25.37(CH_3)
8	48.26	67.25	126.37-142.10	---
9	47.29	66.25	124.37-146.02	---
10	48.02	66.36	125.36-146.28	---
11	47.83	66.21	121.25-139.36	---
12	47.16	67.32	121.85-138.32	---
13	47.21	67.29	121.90-139.38	---
14	47.15	67.78	121.28-141.37	45.29 $N(CH_3)_2$
15	47.27	66.84	118.44-139.24	---
16	47.17	66.28	115.35-158.71	59.27(OCH_3)
17	47.15	66.31	114.18-148.41	24.27(CH_3)
18	47.86	66.76	115.25-159.19	---
19	48.21	66.32	116.40-157.29	---

The effect of solvents on the yield was also studied with methanol, ethanol, dichloromethane and tetrahydrofuran from each component of the catalyst (entry 10). Similarly the effect of microwave irradiation was studied on each component of the catalyst. The effect of solvents on the yield of oxazine derivatives was presented in Table 3. From the table highest yield of oxazine obtained from the cyclization of chalcones andurea with the catalyst fly-ash:H_2SO_4 in microwave irradiation. The infrared andnmr spectroscopic data of these oxazines amines are summarized in Table 4.

CONCLUSION

Some oxazine amine derivatives including 2-naphthyl based oxazine amines have been synthesised by solvent free cyclization of aryl chalcones and urea in presence of fly-ash:H_2SO_4 catalyst undermicrowave irradiation. This synthetic methodology offers solvent-free environmentally benign cyclization, non-hazardous, shorter reaction time, easy-workup procedure and better yields. The analytical and spectral data were supported for these oxazine derivatives.

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