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Research Article

Greener, Simple and Efficient Synthesis of Some Oxazine-2-amine Derivatives by Preheated Fly-Ash Catalyzed Cyclization of Aryl Chalcones under Solvent-Free Conditions

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Abstract. To synthesize some aryl oxazine amines including 4-(4-methoxy-1-naphthyl)-6-(substituted phenyl)-4H-5,6-dihydro-1,3-oxazine-2-amines by preheated fly-ash catalyzed solvent-free cyclization of aryl chalcones and urea under microwave irradiation, the yields of the oxazines were more than 50%. These oxazine imines were characterized by their physical constants and spectroscopic data.

Keywords: Oxazine-2-amines; Chalcones; Preheated fly-ash; Environmentally benign reaction

1. Introduction

Compounds containing one oxygen and one nitrogen atom in the six membered heterocyclics are known as unsaturated 1,3-oxazine or generally oxazines [1, 2]. These oxazine molecules include many isomeric structures such as 1,2 or 1,3 or 1,4 oxazine types [3] depending upon the relative position of these tow atoms and the double bond. These oxazines were medicinally important due to the presence of oxygen and nitrogen heteroatoms along with a double bonds in their structural moieties [4]. The important medicinal activities of these oxazine derivatives are anti-bacterial [4, 5], 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 kinase beta [19] and PTP-1B inhibition [20]. These oxazine derivatives were applied for improving the super resolution microscope [21], synthesis of eosinophils [22], and 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 oxazine derivatives [25]. Nowadays scientists, organic chemists, are interested in solvent-free

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

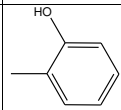
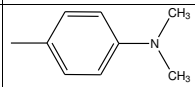
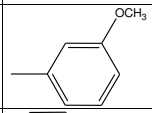
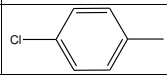
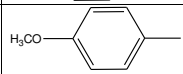
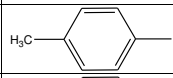
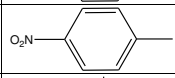
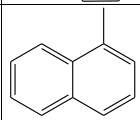
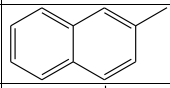
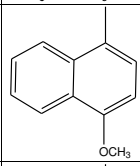
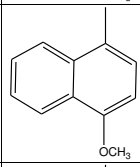
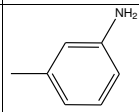
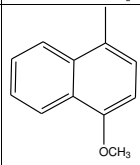
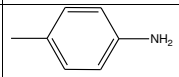
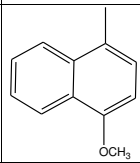
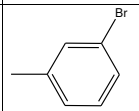
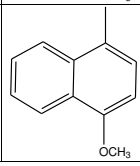
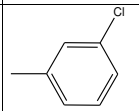
Entry	R	R′	M.W.	Yield (%)	m.p.(°C)	Mass (m/z)
1			252	54	134–136	252[M$^+$], 236, 175, 160, 84, 77, 43, 42, 16
2			268	55	144-145 (145–146)[5]	268[M$^+$], 252, 251, 236, 175, 160, 99, 93, 84, 77,43, 42, 16
3			295	56	65-66 (65–66)[5]	295[M$^+$], 280, 265, 279, 251, 236, 175, 160, 118, 84, 77, 44, 43, 42, 30, 16, 15
4			282	50	122–123	282[M$^+$], 266, 251, 236, 205, 190, 175, 160, 107, 91, 84, 77, 43, 42, 31, 16
5			288	55	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	58	112–113	266[M$^+$], 251, 250, 175, 160, 91, 84, 77, 43, 42, 31, 16, 15
8			297	55	141–142	297[M$^+$], 281, 251, 175, 168, 160, 122, 84, 77, 45, 43, 42, 16
9			302	57	98–99	302[M$^+$], 286, 225, 210, 159, 127, 99, 84, 77, 52, 43, 42, 16
10			302	56	109–110	302[M$^+$], 286, 320, 301, 278,259, 225, 175,161, 127, 99, 91, 84, 77, 52, 43, 42, 35,16
11			332	60	124–125	332[M], 317, 316, 305, 255,225, 210, 175, 168, 157, 124, 99, 91, 84, 77, 59, 43, 42, 31, 16,15
12			347	54	105–106	347[M$^+$], 331, 316, 255, 198, 190, 175, 168, 157, 134, 92, 91, 77, 43, 42, 31, 16, 15,
13			347	55	125–126	347[M$^+$], 331, 255, 198, 175, 168, 157, 92, 91, 77, 43, 42, 31, 16, 15
14			411	55	98–99	411[M$^+$], 413[M^{2+}], 331, 316, 255, 240, 210, 157, 154, 91, 84, 77, 43, 42, 31, 16, 15
15			366	54	128–129	366[M$^+$], 368[M^{2+}], 335, 331, 278, 255, 209, 182,168, 157, 154, 127, 111, 99, 91, 77, 58, 35, 31, 16, 15

Table 1: Continued.

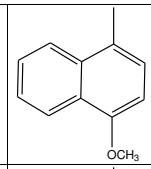
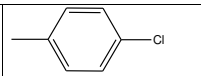
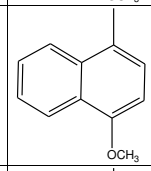
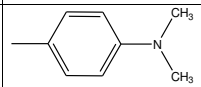
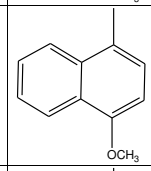
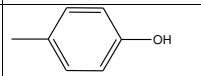
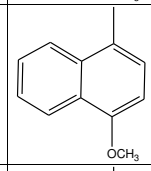
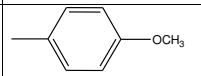
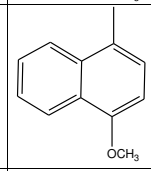
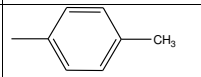
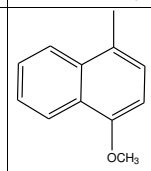
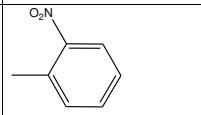
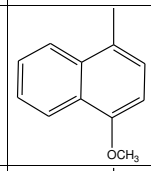
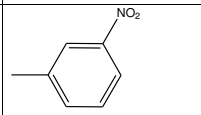
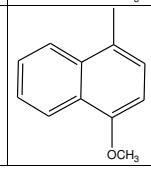
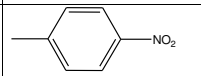
16			366	55	113–114	366[M$^+$], 368[M^{2+}], 335, 331, 278, 255, 182,168, 157, 127, 111, 91, 77, 58, 43, 42, 35, 31, 16, 15
17			375	58	110–111	375[M$^+$], 360, 359, 345, 344, 331, 255, 218, 203, 161, 157, 120, 99, 91, 77, 44, 43, 42, 31, 30,16, 15,
18			348	54	121–122	348[M$^+$], 332, 331, 317, 255, 191, 157, 127, 99, 93, 91, 77, 58, 42, 31, 17, 16, 15,
19			362	61	124–125	362[M$^+$], 347, 331, 304, 255, 205, 198, 164, 157, 107, 93, 91, 77, 58, 43, 42, 31, 16,15,
20			346	60	116–117	346[M$^+$], 331, 330, 315, 255, 189, 157, 15, 99, 93, 91, 77, 58, 43, 42, 31, 16, 15,
21			377	52	128–129	377[M$^+$], 361, 346, 331, 319, 255, 220, 212, 205, 198, 179, 165, 157, 122, 91, 84, 77, 58, 46, 43, 41, 31, 16, 15
22			377	55	117–118	377[M$^+$], 361, 346, 331, 319, 255, 220, 205, 198, 165, 157, 91, 84, 77, 46, 43, 41, 31, 16, 15
23			377	55	133–135	377[M$^+$], 361, 331, 319, 255, 220, 212, 198, 179, 165, 157, 91, 84, 77, 58, 43, 41, 31, 16, 15

Table 2: Reusability of preheated fly-ash catalyst on cyclization of styryl 4-methoxy-1-naphthyl ketone (2 mmol) with urea (2 mmol) under microwave irradiation(**entry 11**).

Run	1	2	3	4	5
Yield	60	60	59.5	59.5	59

Table 3: The effect of solvents in conventional heating and without solvent in microwave irradiation on yield of oxazine amine (**entry 11**).

Solvents				MW
MeOH	EtOH	DCM	THF	
45	51	55	50	60

MeOH = Methanol; EtOH = Ethanol; DCM = Dichloromethane; THF = Tetrahydrofuran; MW = Microwave.

synthesis [6, 26–30]. Some reactions such as hetero Diels-alder reaction [4], ring closure [31], Betti base induced condensation [32], Mannich type condensation-cyclization [6] and cyclization of chalcones[5] were used for synthesis of oxazine derivatives. Verma et al. [26] have synthesised some

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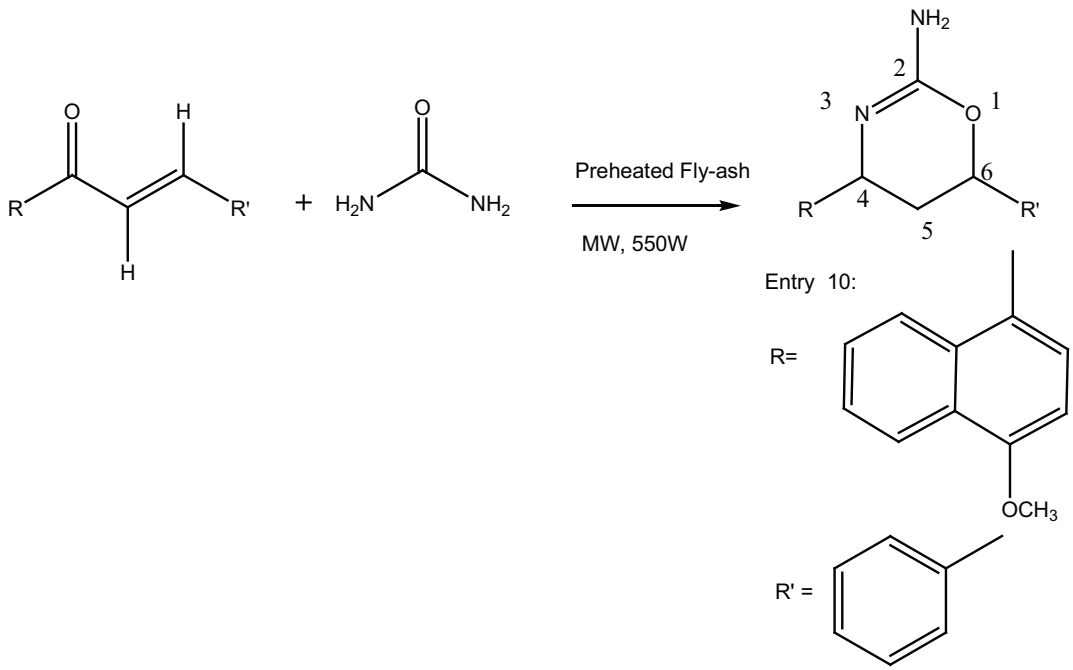
Table 4: Infrared and NMR spectroscopic data of 4-aryl-5,6-dihydro-6(substituted phenyl)-4H-1,3-oxazine-2-amines.

Entry	IR(ν, cm^{-1})				^{1}H(δ, ppm)							^{13}C(δ, ppm)		^{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)	Ar-H, m	Substt.	C_2	C_4	C_5	C_6	Ar-C	Substt.
1	3534	1598	1234	—	2.345	2.625	2.425	2.214	4.257	6.545-7.345	—	165.33	52.56	47.33	65.90	125.36-142.25	—
2	3564	1628	1245	3564(OH)	2.295	2.598	2.465	2.201	4.351	6.289-7.258	—	164.82	51.36	47.98	66.25	126.25-139.38	—
3	3526	1614	1264	—	2.214	2.491	2.458	2.269	4.451	6.358-7.298	3.658(s, $N(CH_3)_2$)	164.35	52.36	47.01	65.98	122.68-139.25	44.38 $N(CH_3)_2$
4	3514	1610	1236	1238(OCH_3)	2.361	2.412	2.542	2.230	4.652	6.257-7.987	4.023(s, CH_3)	164.03	52.28	48.74	65.39	121.36-141.25	62.38 (OCH_3)
5	3536	1599	1265	—	2.173	2.918	2.350	2.113	4.714	7.174-7.291	—	164.17	52.07	47.95	67.03	126.43-139.40	—
6	3525	1621	1218	1225(OCH_3)	2.277	2.753	2.299	2.217	4.593	6781-7.352	3.997(s,OCH_3)	163.21	52.19	47.94	66.79	114.54-137.36	56.78(OCH_3)
7	3535	1597	1216	—	2.187	2.811	2.246	2.176	4.669	6.956-7.378	2.536(s, CH_3)	164.90	52.76	47.17	66.84	125.77-139.04	25.37(CH_3)
8	3558	1624	1265	—	2.317	2.897	2.436	2.223	4.709	7.273-8.165	—	165.23	52.78	48.26	67.25	126.37-142.10	—
9	3523	1589	1212	—	2.295	2.384	2.201	2.236	4.652	6.259-7.962	—	164.99	51.36	47.29	66.25	124.37-146.02	—
10	3526	1598	1215	—	2.291	2.301	2.221	2.245	4.252	6.325-7.852	—	165.02	52.01	48.02	66.36	125.36-146.28	—
11	3556	1597	1215	—	2.283	2.311	2.223	2.256	4.246	6.312-7.854	—	165.33	52.57	47.67	66.34	121.57-139.87	—
12	3545	1592	1215	—	2.116	2.249	2.223	2.326	4.672	6.556-7.989	4.897(s, NH_2)	165.36	52.78	47.20	67.37	121.67-138.89	—
13	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	47.26	67.33	121.80-139.43	—
14	3545	1605	1215	—	2.225	2.219	2.265	2.025	4.632	6.725-7.787	—	164.25	52.65	47.20	67.66	121.24-141.39	—
15	3535	1589	1222	—	2.125	2.258	2.264	2.038	4.671	6.825-7.887	—	165.28	52.87	47.35	66.89	118.46-139.67	—
16	3555	1608	1215	—	2.112	2.232	2.322	2.154	4.776	6.667-7.946	3.765	164.87	52.32	47.43	66.56	118.57-139.79	—
17	3545	1610	1210	—	2.091	2.225	2.356	2.178	4.798	6.632-7.946	3.787(s, $N(CH_3)_2$)	164.98	52.90	47.10	67.65	121.20-141.31	45.12 $N(CH_3)_2$
18	3555	1586	1220	—	2.212	2.323	2.334	2.167	4.238	6.676-7.898	—	165.76	52.90	47.23	66.47	118.43-139.29	—
19	3535	1615	1210	1215(OCH_3)	2.221	2.235	2.342	2.116	4.378	6.836-7.987	4.237(s,OCH_3)	164.65	52.79	47.10	66.16	115.30-158.68	59.08(OCH_3)
20	3540	1623	1212	—	2.216	2.234	2.256	2.138	4.487	6.290-7.865	2.30(CH_3)	164.90	52.53	47.15	66.36	114.54-148.67	24.27(CH_3)
21	3558	1626	1216	—	2.325	2.238	2.336	2.123	4.628	6.835-7.576	—	165.39	52.26	47.89	66.88	115.67-159.78	—
22	3550	1605	1210	—	2.326	2.237	2.387	2.179	4.635	6.866-7.589	—	165.46	52.39	47.85	66.79	115.78-159.99	—
23	3555	1649	1220	—	2.189	2.210	2.329	2.026	4.639	6.524-7.996	—	165.34	52.86	48.29	66.39	116.49-157.99	—



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

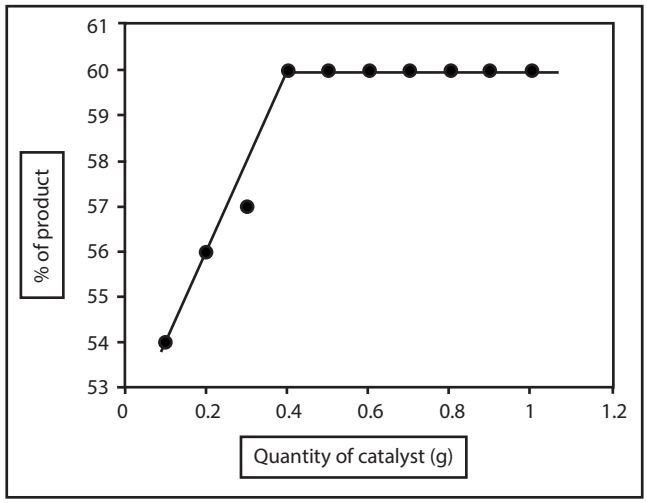


Figure 1: The effect of catalyst loading.

benzoxazine/oxazine fused isoquinolines and naphthyridines by solvent-free method. Elarfi and Al-Difar [5] have synthesised some 1,3-oxazine derivatives by solvent-assisted method from chalcones and urea. More than 75% yield of dihydro-^{2}H-benzo- and naphtho-1,3-oxazine derivatives were prepared by [6] using eco-friendly method. Efficient synthesis of some 1,3-oxazine-4-thiones were synthesised by N-methyl imidazole 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[31]. Within the above view, there is no information available in the literature for the solvent-free synthesis of 4-methoxy-1-naphthyl based oxazine-2-amine derivatives. Therefore the author has taken effort to synthesize some 4-methoxy-1-naphthyl based oxazine amines characterized by their analytical and spectral data.

2. Materials and Methods

2.1. General. All chemicals 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 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.

2.2. Preparation of preheated fly-ash [33]. The fly-ash was heated on hot air oven at 110˚C for 2h. During heating demoisturising takes place. This preheating helps avoiding colloidal formation during the reaction.

2.3. Synthesis of 4-(aryl)-5,6-dihydro-6-(substituted phenyl)-4H-1,3-oxazine-2-amines. Equimolar quantities of chalcones (2 mmol), urea (2mmol) and 0.4 g of preheated fly-ash were taken in a 50 mL beaker, closed with the lid. This mixture was subjected to microwave irradiation for 2–4 minutes at 650W (Scheme 1) (Samsung, Microwave Oven, 100–700W). After completion of the reaction, dichloromethane (20 mL) was added, followed by simple filtration. The solution was concentrated and purified by recrystallization. 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.

3. Results and Discussion

The author attempts to synthesize oxazine derivatives by cyclization of chalcones possessing electron withdrawing as well as electron donating group as substituents, urea and in the presence of acidic catalyst preheated fly-ash using microwave irradiation. Hence the author has synthesized some substituted 1,3-oxazine derivatives by the cyclization of 2 mmole of chalcone, 2 mmole of urea under microwave irradiation with 0.4g of preheated fly-ashcatalyst 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 preheated fly-ash 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 4-methoxy-1-naphthyl ketone (entry 11) and urea under the same condition as above. In this reaction the obtained yield was 60%. 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 52 to 60%. Considering 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 Figure 1. The optimum quantity of catalyst loading was found to be 0.4 g. The reusability of this catalyst was studied for the cyclization of styryl 4-methoxy-1-naphthyl ketone and urea (entry 11) is presented in Table 2. From Table 2, first two runs gave 60% product. The third, fourth and fifth runs of reactions gave, respectively, the yields 59.5%, 59.5% and 59% of oxazines. There was no appreciable loss in its effect of catalytic activity observed up to fifth run. The effect of solvents on the yield was also studied with methanol, ethanol, dichloromethane and tetrahydrofuran from each component of the catalyst (entry 11). 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 is obtained from the cyclization of chalcones and urea with the catalyst preheated fly-ash in microwave irradiation. The infrared and nmr spectroscopic data of these oxazine-2-amines are summarized in Table 4.

4. Conclusions

Some oxazine-2-amine derivatives including 4-(4-methoxy-1-naphthyl)-5,6-dihydro-6- (substituted phenyl)-4H-1,3-oxazine-2-amines have been synthesised by solvent-free cyclization of aryl chalcones and urea in presence of preheated fly-ash catalyst under microwave irradiation. This synthetic methodology offers solvent-free cyclization, nonhazardous, shorter reaction time, easy-workup procedure and better yields. The analytical and spectral data were supported for these oxazine derivatives.

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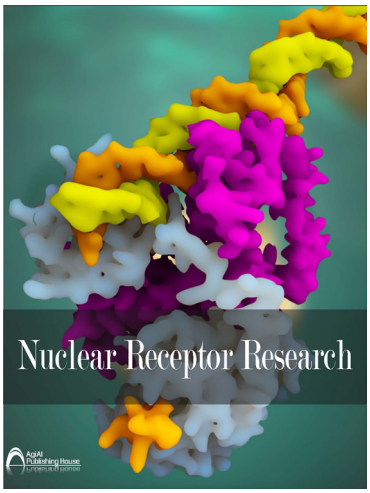

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