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Microwave induced novel synthesis and characterization of 3,5-diaryl-Δ^2-isoxazoline" from α, β-unsaturated carbonyl compounds

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Abstract

A facile one-pot synthesis of some "3,5-diaryl-Δ^2-isoxazoline" from α,β-unsaturated carbonyl compounds and hydroxyl amine hydrochloride in presence of alkali/basic(Al_2O_3)using MWI. For the synthesis of isoxazolines basic alumina as inorganic solid supports have been developed. The time of reaction has been brought down from hrs. to minutes with increase in yield compared to classical method, demonstrating the versatility of the process. MWI synthesis of 3,5-diaryl-Δ^2-isoxazoline with basic alumina was found better solid support in comparison to silica gel with easy experimental manipulation. The structures of synthesized compounds have been characterized by spectral studies.

Keywords: Microwave, α,β-unsaturated carbonyl compounds, Hydroxyl amine hydrochloride, Basic Al_2O_3, Antimicrobial activity.

Introduction

Compounds incorporating oxygen and nitrogen containing heterocyclic ring system are of considerable interest due to wide range of microbial activities they possess. Five member heterocyclic compounds among them occupy a unique place in the field of natural and synthetic organic chemistry. Five membered heterocyclic compounds like isoxazolines have wide application as agro chemical and pharmaceutical agents. Recently attention has increasingly been given to the synthesis of isoxazolines derivatives as source of new antimicrobial agents[1]. Therefore synthesis of new isoxazolines derivatives remains a main focus of medicinal research. The chemistry of α,β- unsaturated carbonyl compounds[2] has been recognized as a significant field of study. Therefore various types of heterocycles have been used for developing import biological molecules like isoxazolines. Chalcones[3] and some amino derivatives of chalcones[4] are important biocides their biological activity due to the α, β-unsaturated carbonyl group, are associated with wide range of biological active compounds. Chalcone being a very good synthon, variety of novel heterocycles members[5] like isoxazoles[5] can be designed with good pharmacological profile.

Material and methods

Structures of the all synthesized compounds 4a-k were confirmed by elemental analysis and spectral data (1H NMR, IR and mass). Further structures of synthesized compounds were established by performing thin layer chromatography on silica gel-G plates using benzene-ethyl acetate (9:1) solvent system as eluent. Digilab FTS-14 or Perkin-Elmer 157P spectrophotometer in KBr (νmax in cm-1) used to recorded IR spectra .1H NMR of compounds was recorded on acetone-d6 on a Brucker DRX-300 (300 MHz) or Varian CFT-20 spectrometer using TMS as internal standard (chemical shift in δ ppm). Jeol SX-102 spectrometer was used to record FAB mass spectra of compounds. Spectral data and elemental analysis data was satisfactory for all compounds. Domestic microwave oven (Kenstar, output energy 1200 W, frequency 2450 MHz, Model No. MO9760)/ was used to carry out all the reactions.

General Method: A facile one-pot synthesis of 3-5-diaryl-Δ^2-isoxazolines (4a-k): Method A: Classical (Conventional) method: α, β-unsaturated carbonyl compound (0.005 mol) was dissolved in ethyl alcohol (25 mL). Hydroxyl amine hydrochloride (0.007 mol) and KOH (0.5 g) were added to this solution. The reaction mixture was heated under reflux in water bath as per mentioned time in Table-2. Thin layer chromatography on silica gel plates employing benzene: ethyl acetate (9:1 v/v) as eluent was used to monitor the progress of reaction. The reaction mixture after cooling was poured in to crushed ice and neutralized with acetic acid. The isoxazoline precipitates were separated by filtration, washed with water and purified by recrystalization from methanol to obtain the analytical samples of (4a-k).

Method-B: Microwave assisted solution phase method: α,β-unsaturated carbonyl compound and hydroxyl amine hydrochloride is mixed in ethanol and KOH .The reaction mixture was irradiated inside a microwave oven at MW-power (300W) for 6-12 minutes. The reaction mixture was cooled, diluted with ice water, acidified with 30% acetic acid. The product precipitates were separated by filtration, washed with

water and purified by recrystallization from methanol to obtain the afforded analytical samples of (4a-k).

Method-C: Microwave assisted solid phase method: Basic alumina (Al_2O_3) as solid inorganic support with constant stirring was added to a mixture of α, β-unsaturated carbonyl compound and hydroxyl amine hydrochloride, in ethanol. Adsorbed material after mixing properly dried in air and placed inside the microwave oven. After microwave heating (50%, 5-8 min.), the reaction mixture was extracted with methanol resulting the substituted 3, 5-diaryl-Δ2-isoxazolines (4a-k).

4a: Anal. Calcd for $C_{15}H_{12}ClNO$ (257.72): C 69.93, H 4.59,Cl 13.74, N 5.42. H_A (dd, 1H) 3.11, H_B (dd, 1H) 3.77, H_X (dd, 1H), 5.50, Ar-H (m) 6.84-7.68, MS [M/z (%)258 (M+, 100), 259 (M+1, 33), 223 (46), 196 (23), 106 (08), 77 (09). Cl/ OH 716, =C-H (sp_2) 3037, -C-H (sp_3) 2930, 2834, C-O-N (in the ring) 1246, C=N1602, C=C/ Ar1513, 1449, Substituted phenyl. 815, 630.

4b: Anal. Calcd for $C_{16}H_{15}NO$ (237.30): C 80.99, H 6.35, N 5.84. H_A (dd, 1H) 3.37, H_B (dd, 1H) 3.79, H_X (dd, 1H), 5.62, CH_3/ $OCH_{3/2}$ (s) 2.3, Ar-H (m) 6.83-7.42, =C-H (sp_2) 3026, -C-H (sp_3) 2939, 2852, C-O-N (in the ring) 1234, C=N1611, C=C/ Ar1523, 1452, Substituted phenyl. 766,709.

4c: Anal. Calcd for $C_{16}H_{15}NO_2$ (253.30): C 75.82, H 5.94, N 5.50. H_A (dd, 1H) 3.23, H_B (dd, 1H) 3.86, H_X (dd, 1H), 5.47, CH_3/ $OCH_{3/2}$ (s) 3.65, Ar-H (m) 6.81-7.30, MS [M/z (%)253 (M+, 100), 255 (M+2, 28), 223 (36), 189 (14), 163 (19), 92 (08). =C-H (sp_2) 3048, -C-H (sp_3) 2942, 2806, C-O-N (in the ring) 1257, C=N1608, C=C/ Ar1519, 1458, Substituted phenyl. 796,711.

4d: Anal. Calcd for $C_{21}H_{17}NO_2$ 315.36: C 79.56, H 79.56, N 4.41. H_A (dd, 1H) 3.18, H_B (dd, 1H) 3.74, H_X (dd, 1H), 5.77, Ar-H (m) 6.78-7.69, =C-H (sp_2) 3022, -C-H (sp_3) 2936, 2825, C-O-N (in the ring) 1248, C=N1606, C=C/ Ar1523, 1439, Substituted phenyl. 819,617.

4e: Anal. Calcd for $C_{21}H_{16}ClNO_2$ 349.81: C 72.01, H 4.58,Cl 10.06, N 3.99. H_A (dd, 1H) 3.26, H_B (dd, 1H) 3.82, H_X (dd, 1H), 5.59, Ar-H (m) 6.93-7.85, Cl/ OH 723, =C-H (sp_2) 3050, -C-H (sp_3) 2931, 2829, C-O-N (in the ring) 1239, C=N1601, C=C/ Ar1525, 1451, Substituted phenyl. 819, 688, 635

4f. Anal. Calcd for $C_{22}H_{19}NO_2$ (329.39): C 80.20, H 5.79, N 4.21. H_A (dd, 1H) 3.18, H_B (dd, 1H) 3.84, H_X (dd, 1H), 5.59, CH_3/ $OCH_{3/2}$ (s) 2.33, Ar-H (m) 6.96-7.91, MS [M/z (%)329 (M+, 100), 330 (M+1, 43), 315 (37), 233 (22), 196 (10), 78 (07). =C-H (sp_2) 3027, -C-H (sp_3) 2929, 2852, C-O-N (in the ring) 1253, C=N1605, C=C/ Ar1523, 1444, Substituted phenyl. 817, 628

4g. Anal. Calcd for $C_{22}H_{19}NO_3$ (345.40: C 76.48, H 5.42, N 4.01. H_A (dd, 1H) 3.32, H_B (dd, 1H) 3.86, H_X (dd, 1H), 5.80, CH_3/ $OCH_{3/2}$ (s) 3.73, Ar-H (m) 6.88-7.35, =C-H (sp_2) 3047, -C-H (sp_3) 2942, 2859, C-O-N (in the ring) 1233, C=N1614, C=C/ Ar1533, 1436, Substituted phenyl. 815, 658

4h. Anal. Calcd for $C_{22}H_{18}ClNO_2$ (363.84): C 72.32, H 4.84,Cl9.69, N 3.79. H_A (dd, 1H) 3.11, H_B (dd, 1H) 3.73, H_X (dd, 1H), 5.49, CH_3/ $OCH_{3/2}$ (s) 5.21, Ar-H (m) 6.92-7.79,Cl/ OH 712, =C-H (sp_2) 3026, -C-H (sp_3) 2944, 2815, C-O-N (in the ring) 1241, C=N1609, C=C/ Ar1513, 1429, Substituted phenyl. 822, 619.

4i. Anal. Calcd for$C_{23}H_{21}NO_2$ (343.41): C 80.33, H 6.12, N 3.99. H_A (dd, 1H) 3.17, H_B (dd, 1H) 3.79, H_X (dd, 1H), 5.54, CH_3/ $OCH_{3/2}$ (s2.36, Ar-H (m) 6.61-7.39, MS [M/z (%)343 (M+, 100), 345 (M+2, 29), 252 (38), 210 (12), 104 (21), 76 (06)). =C-H (sp_2) 3035, -C-H (sp_3) 2936, 2839, C-O-N (in the ring) 1248, C=N1612, C=C/ Ar1533, 1451, Substituted phenyl. 829, 636.

4j. Anal. Calcd for $C_{23}H_{21}NO_3$ (359.42: C 76.81, H 5.78, N 3.86. H_A (dd, 1H) 3.21, H_B (dd, 1H) 3.80, H_X (dd, 1H), 5.64, CH_3/ $OCH_{3/2}$ (s) 3.81, Ar-H (m) 6.92-7.81, MS [M/z (%)360 (M+, 100), 361 (M+1, 26), 328 (37), 212 (11), 90 (10), 77 (05)=C-H (sp_2) 3056, -C-H (sp_3) 2936, 2839C-O-N (in the ring) 1249, C=N1616, C=C/ Ar1529, 1456, Substituted phenyl. 829, 698, 645.

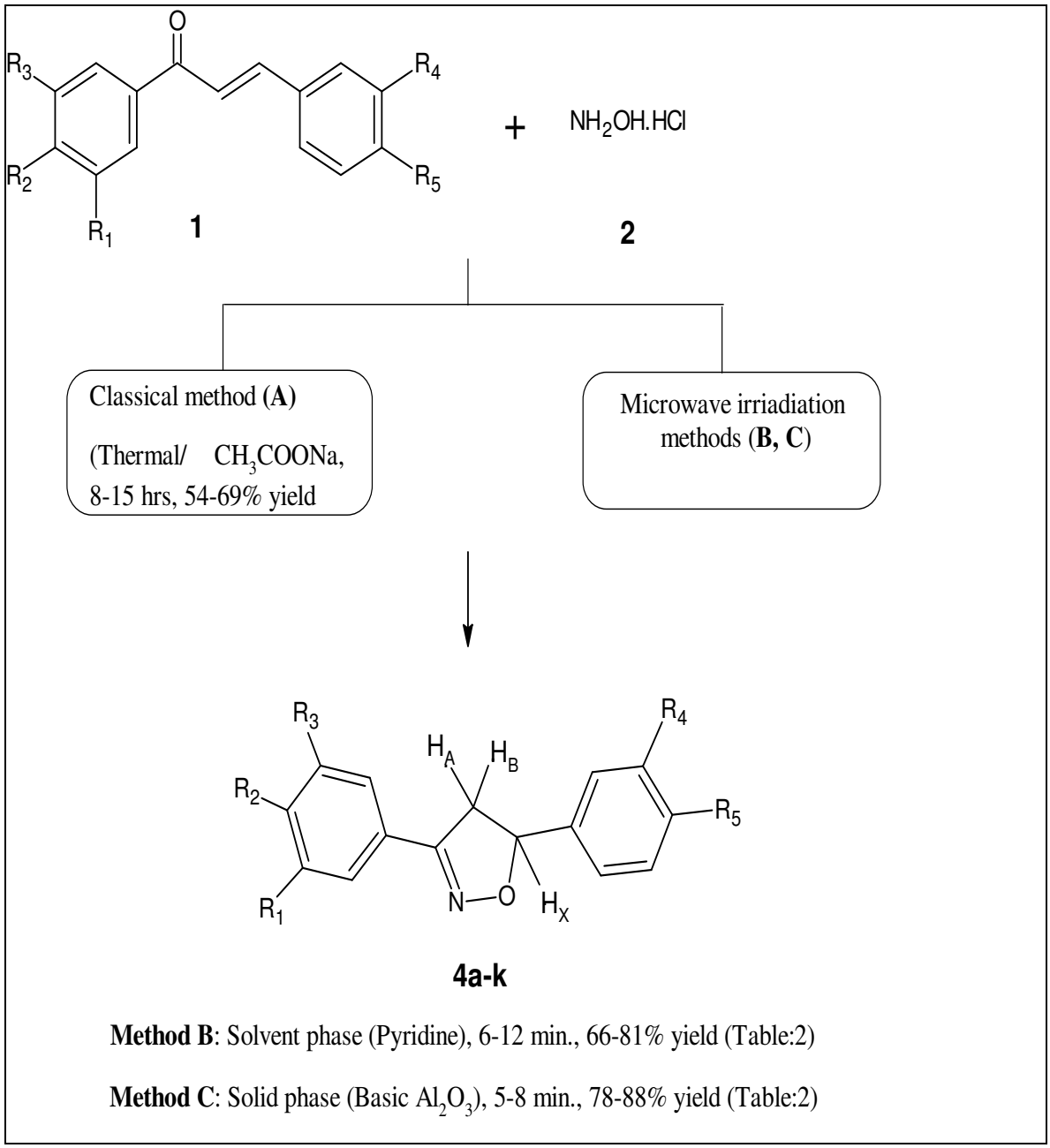
4k. Anal. Calcd for $C_{21}H_{15}Br_2N_3$ (489.16): C 51.51, H 3.00, N 2.81. H_A (dd, 1H) 3.34, H_B (dd, 1H) 3.87, H_X (dd, 1H), 5.73, CH_3/ $OCH_{3/2}$ (s) 3.81, Ar-H (m) 6.84-7.42, Phenolic H(s) /8.26,Cl/ OH 3442 (b), =C-H (sp_2) 3026, -C-H (sp_3) 2926, 2824, C-O-N (in the ring) 1232, C=N1626, C=C/ Ar1536, 1429, Substituted phenyl. 826, 688, 636.

Results and discussion

Isoxazolines are synthesized by several methods available in the literature. These methods are not very satisfactory due to some drawbacks such as higher reaction temperature, longer reaction time, low yield, use of expensive toxic reagent and complicated work-up procedures. Therefore, to develop new methods with greater yields, better efficacy and straightforward procedure is still desirable. During the past decades chemists have been compelled by environment consciousness to make a new twist on an old theme. In this endeavor solid supported reagents have made a landmark and made significant contribution in reducing the waste effluent and preserve the green environment[6-7]. Reactions became easier in dry media with the development of microwave ovens[8-10]. Microwave gives higher yields due to their high heating efficiency, remarkable rate enhancement, greater selectivity and ease of workup. Recently due to the environmentally benign role of solvent free approach using microwave and bioactivity of 3,5-diaryl-Δ^2-isoxazoline prompted us to work towards green synthesis. We reported a facile one-pot rapid condensation of substituted α,β-unsaturated carbonyl compounds (chalcones)[11] with hydroxylamine hydrochloride to prepare substituted 3,5-diaryl-Δ^2-

isoxazoline(**4a-k**) respectively in presence of inorganic solid base/ basic alumina under irradiation microwave.

In classical method 3,5-diaryl-Δ^2-isoxazolineis obtained under different conditions by refluxing α, β-unsaturated ketones[12-13] (**1**) with hydroxyl amine hydrochloride (**2**) in base. Generally refluxing is carried out for 8-15 hrs. This classical method is time consuming, give low yield, tedious, and requires large amount of solvent. Therefore to develop new environmentally benign synthetic method, reactions were carried over basic alumina using microwave induced[14] under solvent free conditions. The both reactants were adsorbed over basic alumina as solid support and irradiated with MW. The yield of reaction was obtained in 78-88% with reaction time 5-8 minutes (Table-2). Solid supports act as both catalysts as well as energy transfer media in reaction. Reaction methods C using basic alumina was found superior to conventional method (method A) or solvent phase MWI (method B). The use of basic alumina in the synthesis 3,5-diaryl-Δ^2-isoxazoline(**4a-k**) was advantageous due to improved yield and easy work up (Reaction Scheme-I).



Scheme-1: Reaction.

The formation of title compounds involve heterocyclisation of substituted chalcones and hydroxyl amine via conjugated Michael addition[15] of nucleophilic attack of electron rich $-NH_2$ group of the hydroxyl amine on the β-carbon atom of the α,β-unsaturated carbonyl compounds followed by dehydration and cyclization and rearrangement under microwave irradiation condition resulted the heterocyclic title compounds 3,5-diaryl-Δ^2-isoxazoline(**4a-k**) through the intermediate formation of Michael adduct (**M.A.**) in a single step.

Antimicrobial Activity: Synthesized compounds (**4a-k**) were tested for their *in vitro* antimicrobial activity against Gram negative *E. coli* and *P. aeruginosa* and Gram-positive *B. subtilis* bacteria as well as antifungal activity against *Candida albicans* and *A. fumigates* fungi at conc. of 200 µg/mL in DMF by the paper disc diffusion method. Their activity was measured by zone of inhibition in mm. Streptomycin and Fluconazole Standard drugs were used as reference compounds. To compare activity of compounds, zone of inhibition of compounds was compared with the standard drugs after incubation of 24 hr of at 25°C. Some compounds showed moderate some showed good activity against the microorganisms used.

Tested compounds 4a, 4c, 4e and 4k showed good to excellent bio activity against all the bacteria and fungi organisms. Tested samples 4a, 4c, 4e and 4k were most effective against *B. subtilis*. From the structural activity relationship (SAR), study it may be revealed that 3,5-diaryl-Δ^2-isoxazoline having chloro and phenoxysubstituent's in phenyl ring have shown excellent result against *E.Coli*. and from the result it may be concluded that the activity of 4a, 4c, 4e and 4k having subsituentschloro, methoxy, phenoxy, dibromo and hydroxyl groups on phenyl ring in 3,5-diaryl-Δ^2-isoxazoline shows important role against B. subtrills. 3,5-diaryl-Δ^2-isoxazoline having methyl, methoxy, hydroxyl, dibromo and phenoxy groups on aryl rings shows excellent antifungal activity tested strains of fungi. The summarized results are given in Table-1.

Conclusion

We have developed a facile rapid one-pot economic methodology for the synthesis of substituted 3,5-diaryl-Δ^2-isoxazoline (**4a-k**) through by the reaction of α,β-unsaturated carbonyl compounds with hydroxyl amine hydrochloride in presence of base/ basic Al_2O_3 using MWI. For the synthesis of isoxazolines (**4a-k**) microwave assisted solid support methodusing basic alumina was found better method in comparison to classical as well as solution phase MWl method and gave shorter reaction time, higher yield and solvent free condition with easy experimental manipulation. The synthesized compound may serve as useful intermediate for the synthesis of structurally diverse heterocyclic compounds. Significant anti-microbial activity was observed with synthesized compounds against bacteria and fungi.

Table-1: Antimicrobial activity of 3,5-diaryl-Δ^2-isoxazoline (zone of inhibition in mm).

S. No.	Comp. No.	Bacteria			Fungi	
		B. subtilis	*E. coli*	*P. aeruginosa*	*A. fumigatus*	*C. albicans*
1	4a	23	25	20	-	-
2	4b	20	14	22	17	16
3	4c	24	16	19	18	10
4	4d	20	22	21	-	-
5	4e	24	23	20	-	-
6	4g	21	16	22	15	13
7	4k	23	20	21	19	17
8	Streptomycin (STD.)	28	28	27	-	-
9	Flucanazole (STD.)	-	-	-	9	17
10	Control (DMF)	00	00	00	00	00

Table-2: Comparison of reaction time and yield of synthesized substituted "3, 5-diaryl-Δ^2-isoxazoline"(4a-4k).

S. No	Chemical name	MP (°C)	Classical Methods* (Thermal/ Pyridine)		Microwave assisted Method** Liquid Media (Pyridine-Solvent)		Microwave assisted Method** Solid Media (Basic alumina)	
			Reaction Time(Hrs)	*% Yield*	*Reaction Time(Min.)*	*% Yield*	*Reaction Time(Min.)*	*% Yield*
4a	3-(phenyl)-5-(4-chlorophenyl)-Δ^2-isoxazoline	129	8.30	65.50	6.50	78.09	5.50	84.25
4b	3-(phenyl)-5-(4-methylphenyl)-Δ^2-isoxazoline	146-148	8.50	69.00	8.00	80.56	6.00	86.53
4c	3-(phenyl)-5-(4-methoxyphenyl)-Δ^2-isoxazoline	139	10.50	56.80	7.50	76.45	6.50	88.15
4d	3-(phenyl)-5-(3-phenoxyphenyl)-Δ^2-isoxazoline	156-158	11.30	63.00	9.50	79.68	7.00	86.65
4e	3-(4'-chlorophenyl)-5-(3-phenoxyphenyl)- Δ^2-isoxazoline	134-136	8.50	56.00	7.50	81.35	7.50	89.35
4f	3-(4'-methylphenyl)-5-(3-phenoxyphenyl)- Δ^2-isoxazoline	158-159	14.00	68.50	12.00	80.50	8.00	85.56
4g	3-(4'-methoxyphenyl)-5-(3-phenoxyphenyl)- Δ^2-isoxazoline	167	9.50	61.35	10.50	76.55	7.50	78.05
4h	3-(4'-chlorophenyl)-5-(4-benzyloxyphenyl)- Δ^2-isoxazoline	116-118	13.00	64.50	9.50	78.50	6.50	86.50
4i	3-(4'-methylphenyl)-5-(4-benzyloxyphenyl)- Δ^2-isoxazoline	192-193	11.50	60.35	9.50	71.76	6.70	79.35
4j	3-(4'-methoxyphenyl)-5-(4-benzyloxyphenyl)-Δ^2-isoxazoline	178-179	13.50	58.85	11.50	69.64	7.80	84.62
4k	3-(3',5'-dibromo-4'-hydroxyphenyl)-5-(3-phenoxyphenyl) - Δ^2-isoxazoline	116-117	15.00	54.50	7.50	66.62	8.20	86.46

The authenticity of the product obtained by method A, B and C was established by mixed m.p., TLC and finally characterized by their elemental analysis and IR, ^{1}H NMR and Mass spectral data.

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