Microwave Assisted Trichloro Triazine Catalyzed Synthesis of 2-(4-((4-Chlorophenyl) Sulfonyl) Phenyl)-5-Phenyloxazoles

Omprakash S. Chavan
P.G., Department of Chemistry Badrinarayan Barwale College, Jalna (MS) 431213, India

Abstract **- Starting as an Amino acid (Hippuric acid) 1 cyclized by using cyanuric acid (TCT) as environmentally benign catalyst to 2-phenyloxazol-5(4H)-one 2 further treated with aromatic aldehyde Friedel-Craft reaction to benzoyl amino ketones 3 and finally cyclized gives good yields of 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-phenyloxazoles 4a-h under microwave condition. The reaction performed in less time of reaction, cleaner no side product, good to excellent yield of product.**

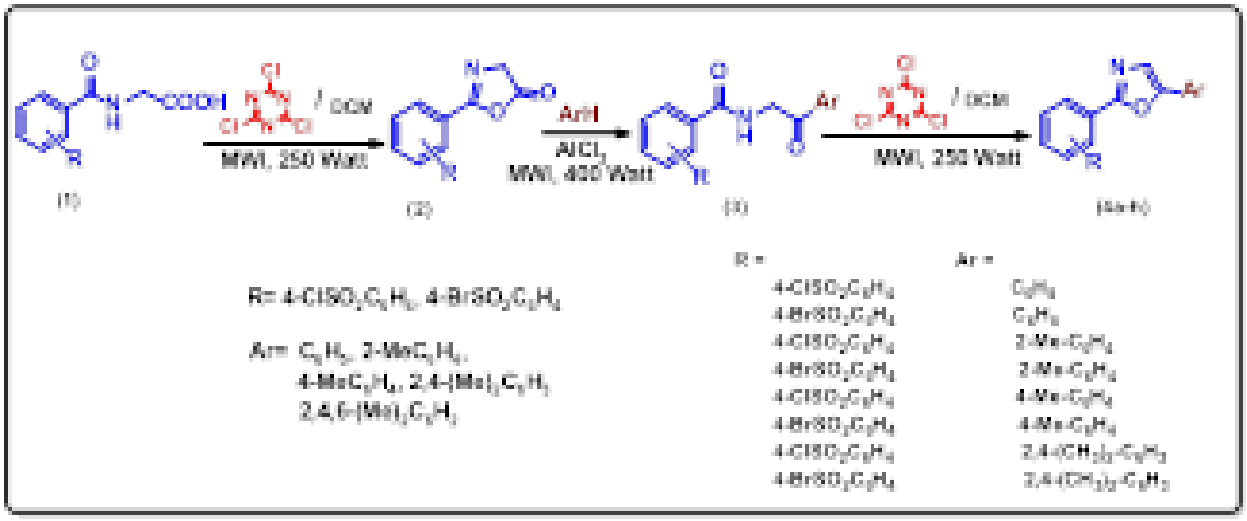
Index Terms **- Hippuric acid, Oxazole, Trichloro triazine (TCT), Microwave method.**

INTRODUCTION

A wide variety of Oxazole based alkaloid such as some natural products [1-2] have been known of their biological properties, for example anti-inflammation [3]. Phenyl substituted oxazoles as having anti-bacterial activity [4]. 2-alkyl and 2-cycloalkyl-4, 5 phenyloxazoles as intermediates used as analgesic and antipyretic activity [5]. 4-substituted chloro- or 4-bromo-benzenesulfonyl)-phenyl] such 2,5-diaryloxazoles 4a-h (Scheme 1) which are potential fluorescent sensors, laser dyes, and scintillators for detecting nuclear radiations [6].

The previously reported method for the synthesis of 2, 5 di-aryl oxazole derivatives using phosphorous oxy halide and other halogenated reagents [7]. The halogenated reagents or catalyst and solvents were toxic and hazardous for human society. It causes huge amount of pollution. To convey these difficulties, it is essential to develop a simple and more eco-friendly method for the synthesis of 2, 5 di-aryl oxazole derivatives using cyanuric chloride (TCT) as environmentally benign catalyst. In addition to microwave irradiation reaction [8], reaction performed cleaner, short reaction time, no side product and good yield of product. In continuation with our interest as a part of green synthetic protocol [9-15], we reported this reaction which performed in less time of reaction, cleaner no side product, good to excellent yields of products.

Scheme 1.Synthesis of Oxazole Derivatives.



RESULT AND DISCUSSION

Initially, we optimized various solvent for the model reaction of Hippuric acid (0.011mol), Cyanuric chloride (0.035mol) and Solvent 10 ml, 100ºC by conventional method and power at 250 W, 48-550C by Microwave method. A very good yield was obtained in a short reaction time under the microwave irradiation method, using dichloro methane as a solvent. While, in Chloroform, dimethyl sulfoxide and toluene corresponding yield was obtained (Table 1 entry 2, 3, 4, 5). If we increase or decrease the time of reaction, there is no significant yield of product. Thus, we decide to carry out reactions in DCM as a solvent in cyanuric chloride as catalyst under both conventional as well as microwave method.

Scheme 2. Plausible Mechanism for Synthesis of 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-phenyloxazole

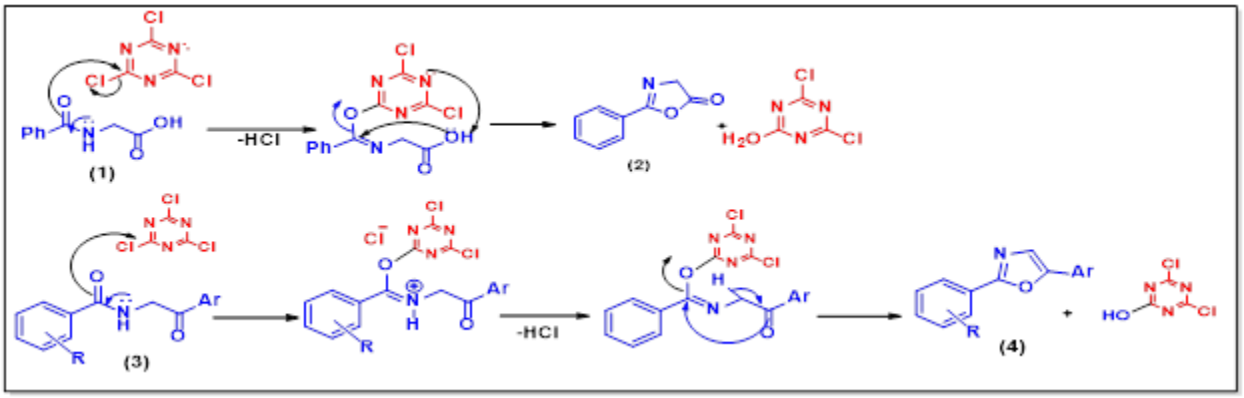


Table 1. Screening of solvents with cyanuric chloride for the synthesis of 2-(4-((4-chlorophenyl) sulfonyl) phenyl) oxazol-5(4H)-one 2a:

Entry	Catalyst	Solvent	Reaction condition							
			Conventional method[a]				Microwave method[a]			
			Time(min)		Yield[b](%)		Time(min)		Yield[b](%)	
			a	b	a	b	a	b	a	b
1.	Cyanuric chloride	DMF	60	70	30	50	2	3	35	58
2.	Cyanuric chloride	DCM	50	60	73	90	2	3	82	98
3.	Cyanuric chloride	Chloroform	60	70	65	89	2	3	78	89
4.	Cyanuric chloride	DMSO	60	70	35	65	2	3	56	71
5.	Cyanuric chloride	Toluene	60	70	32	58	2	3	48	66
6.	Cyanuric chloride	Ethanol	60	120	28	40	2	3	35	52
7.	Cyanuric chloride	Water	60	120	00	00	3	5	00	00

A Conventional Method reaction condition: Hippuric acid(0.011mol), Cyanuric chloride (0.035 mol) and Solvent 10ml, 100ºC. a Microwave Method reaction condition: Hippuric acid(0.011mol), Cyanuric chloride (0.035 mol) and Solvent 10ml, power at 250 W, 45-55ºC, bIsolated yield.

For the second model reaction of 4-((4-chlorophenyl) sulfonyl) -N-(2-oxo-2-phenylethyl) benzamide (0.022mmol) 3a, cyanuric chloride (0.044mmol) and solvent 15ml, microwave method-400 watt. 110 ºC good yield was obtained in a short reaction time using dichloromethane (DCM) as a solvent in appropriate time of reaction (Table 2 entry 2). While, in dimethyl form amide (DMF), chloroform, dimethyl sulfoxide, toluene gave corresponding yield and ethanol gave very poor yield (Table 1 entry 1, 3, 4, 5, 6).

If we increase or decrease the time of reaction, there is no significant effect on yield of product. The cleaner reaction performed in less time of reaction by microwave irradiation method.

Thus, we decide to carry out reactions in DCM as a solvent in cyanuric chloride as catalyst under microwave method. All the examples were tested

reasonably good to excellent yield (Table 3). Here, we used by replacing hazardous, toxic organic solvents and reagent or catalyst. This is one of the most important goals in Green synthesis. Finally, synthesized products were characterized by FT-IR instrument, (υ max in cm-1), 1HNMR spectra were recorded on a Bruker spectrometer 300 MHz and 75 MHz for 13C-NMR spectra. Chemical shifts are reported as δ ppm units and compared with those reported method [7b].

Table 2. Screening of solvents with cyanuric chloride for the synthesis 2-(4-((4-chlorophenyl)sulfonyl)phenyl)-5-phenyloxazole 4a:
chlorophenyl)sulfonyl)phenyl)-5-phenyloxazole 4a:

Entry	Catalyst	Solvent	[a]Reaction condition			
			Time(min)		Yield[b] (%)	
			a	b	a	b
1.	Cyanuric chloride	DMF	5	6	30	50
2.	Cyanuric chloride	DCM	4	5	98	93
3.	Cyanuric chloride	Chloroform	4	5	62	73
4.	Cyanuric chloride	DMSO	4	5	60	69
5.	Cyanuric chloride	Toluene	5	6	56	63
6.	Cyanuric chloride	Ethanol	6	6	38	36
7.	Cyanuric chloride	Water	8	7	00	00

[a]Conventional Method reaction condition : 4-((4-chlorophenyl)sulfonyl)-N-(2-oxo-2-phenylethyl)benzamide (0.022mmol) 3a, Cyanuric chloride (0.044mmol) and Solvent 15ml, MWI, 100ºC;
[b]Isolated yield.

Table 3. Synthesis of Substituted 2, 5-Diphenyloxazoles (4) with respect to yield of reaction, time, physical constant of obtained products.

Sr. no.	Compound	R	Ar	Time(min)/ Yield(%)	M.P.(ºC) Found	M.P.(ºC) Reported[7b]
1	4a	4-$ClSO_2C_6H_4$	C_6H_5	4/98	201-102	200
2	4b	4-$BrSO_2C_6H_4$	C_6H_5	4/94	184-186	185
3	4c	4-$ClSO_2C_6H_4$	4-Me-C_6H_4	5/95	235-236	236
4	4d	4-$BrSO_2C_6H_4$	4-Me-C_6H_4	5/93	233-234	235
5	4e	4-$ClSO_2C_6H_4$	2,4-$(Me)_2$-C_6H_3	5/91	152-153	153
6	4f	4-$BrSO_2C_6H_4$	2,4-$(Me)_2$-C_6H_3	5/90	200-202	202
7	4g	4-$ClSO_2C_6H_4$	2,4,6-$(Me)_2$-C_6H_3	5/93	164-165	164
8	4h	4-$BrSO_2C_6H_4$	2,4,6-$(Me)_2$-C_6H_3	5/92	179-180	179

[a]Microwave Method reaction condition: Comp 3 (0.011mol), Cyanuric chloride (0.044 mol) and DCM (15 ml), power at 250 W, 100ºC, [b]Isolated yield.

EXPERIMENTAL SECTION

General:

Starting materials were commercially available. The major chemicals were purchased from Sigma Aldrich fine chemicals. Reaction courses were monitored by TLC on silica gel recoated F_{254} Merck plates. Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected, with a Perkin-Elmer Lambda spectrophotometer. IR spectra were recorded with an FT-IR instrument, (υ_{max} in cm^{-1}), ^{1}HNMR spectra were recorded on a Bruker spectrometer 300 MHz and 75 MHz for ^{13}C-NMR spectra. Chemical shifts are reported as δ ppm units.

General procedure for the synthesis of Oxazolone or Cyclization of Hippuric acid (2a):

Conventional Method:

A mixture of hippuric acid (0.011mol) 1a, cyanuric chloride (0.035mol) and dichloromethane (10ml) was added and the contents of solution was stirred and

heated to 50ºC for the appropriate time (Table 1). Progress the reaction was monitored by thin layer chromatography (ethyl acetate: n-hexane). The solid obtained, crystallized from ethyl alcohol, colourless crystal of compound 2a. Yield= 83%

Microwave Method:
A mixture of hippuric acid (0.011mol) 1a, cyanuric chloride (0.035mol) and dichloromethane (10ml) was added and the contents of solution were subjected to microwave irradiation programmed at 250 watt, 45-50 ºC for the appropriate time (Table 1). Progress the reaction was monitored by thin layer chromatography (ethyl acetate: n-hexane). The solid obtained, crystallized from ethyl alcohol, colourless crystal of compound 2a.

General procedure for the synthesis of 4-((4-chlorophenyl) sulfonyl)-N-(2-oxo-2-phenylethyl) benzamide(3a):
Microwave Method:
The azalactone (5mmol) 2a in 25 ml of toluene or xylene in excess amount was added portion wise with (15mmol) of anhydrous aluminium chloride at room temperature. After the addition, the reaction of mixture was irradiated under microwave at 400-watt 110ºC for 12-15 min. Progress the reaction was monitored by thin layer chromatography (ethyl acetate: n-hexane). The reaction mixture was then poured over crushed ice with hydrochloric acid and the organic component was extracted with ethyl acetate, washed with water and dried. The solvent was removed under the vacuum pressure and finally the product was crystallized from ethyl alcohol colourless needle was obtained.

General procedure for the synthesis of Substituted 2, 5-diphenyloxazoles 4:
Microwave Method:
A mixture of 4-substituted N-(2-oxo-2-phenylethyl) benzamide (0.022mmol) 3, cyanuric chloride (0.044mmol) and dichloromethane (15ml) was added and the contents of solution subjected to the microwave irradiation for programmed at 250 watt, 100ºC for 4-5 min. Progress the reaction was monitored by thin layer chromatography (ethyl acetate: n-hexane), washed with water followed by sodium bicarbonate. The solid obtained, crystallized from ethyl alcohol.

Spectral Characterization Data:(2a) 2-(4-((4-chlorophenyl) sulfonyl) phenyl) oxazol-5(4H)-one:
Yield= 95%; mp: 181-182ºC; for $C_{15}H_{10}ClNO_4S$.; FTIR (cm^{-1}) 1816(C=O), 1665(C=N), 1152, 1322 (SO_2); ^{1}HNMR (δppm, DMSO-d6); 8.16(d, 2H, *J*= 8.2); 8.12 (d, 2H, *J*= 8.3); 8.06 (d, 2H, *J*= 8.6), 7.72 (d, 2H, *J*= 8.6), 4.62 (s, 2H); ^{13}C-NMR (δppm, DMSO-d6); 170.79, 165.18, 143.78, 139.41, 139.8, 136.63, 129.96, 129.42, 128.59, 128.15, 55.19.

(3a) 4-((4-chlorophenyl) sulfonyl)-N-(2-oxo-2-phenylethyl) benzamide:
Yield=89% and mp: 202-204ºC for $C_{21}H_{16}ClNO_4S$.; FTIR (cm^{-1}) 3389(NH), 1648, 1692(C=O), 1152, 1324 (SO_2); ^{1}HNMR (δppm, DMSO-d6); 7.73(d, 2H, *J*= 8.6); 8.00-8.12 (m, 2H); 8.12 (d, 2H, *J*= 9.0), 8.09 (d, 2H, *J*= 9.0), 9.16 (t, *J*= 5.5), 4.81 (d, *J*= 5.5),; ^{13}C-NMR (δppm, DMSO-d6); 170.79, 165.18, 143.78, 139.41, 139.8, 136.63, 129.96, 129.42, 128.59, 128.15, 55.19.

(4a) 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-phenyloxazole:
Yield=98%; mp: 201-202ºC for $C_{21}H_{14}ClNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 7.40-8.05 (m, 5H,Ar-H); 7.92 (d, 2H, Ar-H), 7.83 (d, 2H,Ar-H), 7.89 (d, 2H, Ar-H), 7.49(d,2H,Ar-H),; ^{13}C-NMR (δppm, DMSO-d6); 161.9, 148.9, 141.2, 139.2, 139.5, 135.3, 129.9, 129.7, 129.5, 129.4, 129.2, 128.5, 128.3, 128.1, 128, 128.7, 125.3, 125.1, 122.3.

(4b) 2-(4-((4-bromophenyl) sulfonyl) phenyl)-5-phenyloxazole:
Yield=94%; mp: 184-186ºC for $C_{21}H_{14}BrNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 7.40-8.05 (m, 5H,Ar-H); 7.91 (d, 2H, Ar-H), 7.86 (d, 2H,Ar-H), 7.73 (d, 2H, Ar-H), 7.68(d,2H,Ar-H),; ^{13}C-NMR (δppm, DMSO-d6); 7.92 (d, 2H, Ar-H), 7.83 (d, 2H,Ar-H), 7.89 (d, 2H, Ar-H), 7.49(d,2H,Ar-H),; ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.6, 141.2, 140.2, 135.5, 135.3, 135, 130.3, 130, 129.7, 129.2, 128.9, 128.7, 128.5, 128.3, 128.1, 128., 128, 125.3, 125.1, 122.2.

(4c) 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-(p-tolyl) oxazole:
Yield=95%; mp: 235-236ºC for $C_{22}H_{16}ClNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 7.63 (d, 2H,Ar-H); 7.22 (d, 2H, Ar-H), 2.30 (s, 1H,

CH_3-Ar), 7.92 (d, 2H, Ar-H), 7.86(d,2H,Ar-H), 7.89(d,2H,Ar-H), 7.48(d,2H,Ar-H); ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.6, 141.2, 139.3, 139, 135.2, 131.3, 129.7, 129.5, 128.3, 129.2, 129.1, 129, 128.7, 128.5, 128.3, 128, 124.5, 124.2, 122.2, 21.2

(4d) 2-(4-((4-bromophenyl) sulfonyl) phenyl)-5-(p-tolyl) oxazole:

Yield=93%; mp: 233-234ºC for $C_{22}H_{16}BrNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 7.63 (d, 2H, Ar-H); 7.23 (d, 2H, Ar-H), 2.32 (s, 3H, CH_3-Ar), 7.82 (d, 2H, Ar-H), 7.92(d,2H, Ar-H), 7.72(d, 2H, Ar-H), 7.68(d, 2H, Ar-H); ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.5, 141.2, 139.2, 139, 135.2, 132.2, 131.3, 129.7, 129.5, 129.2, 129.2, 129, 128.4, 128.3, 128.3, 128, 124.2, 124.2, 122.1, 21.2

(4e) 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-(2,4-dimethylphenyl) oxazole:

Yield=91%; mp: 152-153ºC for $C_{23}H_{18}ClNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s, 1H, N-CH=CH); 7.52 (s, 1H, Ar-H); 7.03 (s, 1H, Ar-H), 7.12 (s, 1H, Ar-H), 2.32 (s, 3H, CH_3-Ar), 2.49 (s, 3H, CH_3-Ar), 7.86 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H); ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.2, 141.2, 139.2, 139, 138.2, 136.3, 135.3, 131.7, 131.3, 129.8, 129.6, 129.4, 129, 128.7, 128.5, 128.3, 128.1, 128.4, 126.2, 122.3, 21.2, 19.1

(4f) 2-(4-((4-bromophenyl) sulfonyl) phenyl)-5-(2,4-dimethylphenyl) oxazole:

Yield=90%; mp: 200-202ºC for $C_{23}H_{18}BrNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 7.52 (s, 1H, Ar-H); 7.02 (s, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 2.31 (s, 3H, CH_3-Ar), 2.48(s, 3H, CH_3-Ar), 7.82 (d, 2H, Ar-H), 7.89(d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.70 (d, 2H, Ar-H); ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.2, 141.3, 138.3, 135.6, 135.1, 132.2, 131.2, 130.3, 130, 128.8, 128.4, 128.2, 128.1, 127.9, 127.5, 126.3, 122.2, 21.3, 19.2

(4g) 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-mesityloxazole:

Yield=93%; mp: 164-165ºC for $C_{24}H_{20}ClNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 2.52 (s, 9H, CH_3-Ar); 6.91 (s, 2H, Ar-H), 7.82 (d, 2H, Ar-H), 7.91(d, 2H, Ar-H), 7.48(d, 2H, Ar-H), 7.86 (d, 2H, Ar-H). ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.2, 141.2, 139.4, 139.1, 138.3, 136.2, 135.5, 135.2, 129.7, 129.5, 129.2, 128.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128, 127.8, 127.2, 21.2, 19.3, 19.1

(4h) 2-(4-((4-bromophenyl) sulfonyl) phenyl)-5-mesityloxazole:

Yield=92%; mp: 179-180ºC for $C_{24}H_{20}BrNO_3S$; ^{1}HNMR (δppm, DMSO-d6); 6.98(s,1H, N-CH=CH); 2.52 (s, 9H, CH_3-Ar); 6.90 (s, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.91(d, 2H, Ar-H), 7.68(d, 2H, Ar-H), 7.71 (d, 2H, Ar-H). ^{13}C-NMR (δppm, DMSO-d6); 161.9, 149.2, 141.2, 140.1, 138.2, 136.2, 135.3, 132.3, 132.1, 130.2, 130, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128, 127.5, 122.2, 21.2, 19.2.

CONCLUSION

In the present work we have developed a new methodology for the synthesis of reported 2-(4-((4-chlorophenyl) sulfonyl) phenyl)-5-phenyloxazole from starting hippuric acid and substituted aromatic compound using trichloro-triazene (TCT) as environmentally benign catalyst in very less time of reaction under the microwave irradiation method. Cleaner reaction profile, no side product, good to excellent yield of product.

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