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ULTRASOUND PROMOTED SYNTHESIS OF BIPHENYLIMIDAZO[2,1B][1,3,4]THIADIAZOLE IN GLYCEROL-WATER

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ABSTRACT:
Biphenylimidazo[2,1-b][1,3,4]thiadiazoles derivatives synthesized by condensation of α-tosyloxyketones and 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine under ultrasound in glycerol and water as environmentally benign medium. Use of ultra sound, Green medium, metal free catalyst free and high percentage yield are the main remarkable feature of this protocol.

KEY WORDS: α--Tosyloxyketones; 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine; Glycerol-H_2O; Ultrasound.

INTRODUCTION:

Imidazothiadiazoles is an nitrogen containing heterocycles exhibit diverse applications in the field of medicinal chemistry such as antitubercular[i-ii], antiulcer[iii], antimicrobial activities[iv,] anxiolytic agents[v], anti-asthmatic[vi], antisecretory[vii-viii], anticonvulsant, analgesic[ix] and anticancer[x] activities.

Use of ultrasound in organic synthesis has emerged as a powerful and well controlled heating source for various organic reactions due to it reduces reaction times and increases the product yields. Ultrasonic irradiation has been extensively utilized to enhance rate of various valuable organic reactions. The majority of the reactions are proceeds through the formation of growth bubbles and collapse of bubbles in an irradiated reaction mixture[xi-xii].

Green solvents in organic synthesis are gaining popularity in organic synthesis especially heterocyclic synthesis because it reduces waste, environmentally benign, increases atom and step economy, avoid laborious work-up procedure and are inexpensive[xiii,xiv,xv]. Glycerol is non-poisonous, inexpensive easily available organic waste, high solubility profile and non-ionic liquid medium of low volatility, stable, recyclable solvent extensively use in organic synthesis[xvi-xvii]. In recent years, majority of methods have been employed for the synthesis of Biphenylimidazo[2,1-b][1,3,4]thiadiazoles; the main part of the protocols involves

cyclocondensation reactions lachrymatric and unstable α-haloaromatic ketones and 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine[xviii]. But, these methods have suffered with serious drawbacks such as low yields, use of lachrymatric and highly irritating unstable α-halo-ketones and laborious workup procedures. Herein, we have developed an efficient and highly expeditious protocol for the one pot synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazole from the coupling of α--tosyloxyketones and 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine in glycerol and water to obtained excellent yield of the products.

EXPERIMENTAL SECTION:

MATERIALS AND METHODS:

All the chemicals and solvents were of AR grade and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. . IR spectra were recorded on JASCO FT-IR-4100 ATR instrument. ^{1}H NMR was recorded using a Bruker spectrometer (400MHz) using tetramethylsilane as an internal standard.

GENERAL PROCEDURE FOR SYNTHESIS OF 2-(BIPHENYL-4-YL)-6-PHENYLIMIDAZO[2,1-B][1,3,4]THIADIAZOLE:

A mixture of α--tosyloxyketones (0.002 mol) and 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine (0.002 mmol) in glycerol-water was irradiated under ultrasound for 15 min. at 85^{o}C. Reaction mixture was poured on crushed ice to obtained solid product with 94-98% yield. Product was recrystallized by ethanol (Scheme 1).

2-(Biphenyl-4-yl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole (3a): ^{1}H NMR δ (ppm) 8.44 (s, 1H, C5-H) and 7.29-8.10 (m, 14H, Ar-H); ^{13}C NMR: δ (ppm) 124.02, 124.19, 125.11,125.84, 126.02,126.11, 127.49,129.12, 132.00, 132.89, 142.22. MS m/z: 253.79 (M+), 254.79 (M+1).

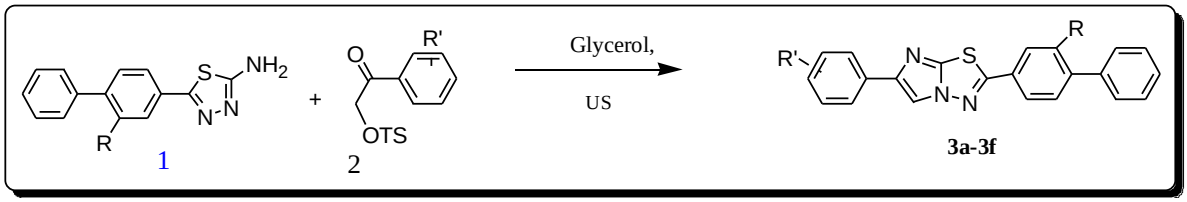
2-(Biphenyl-4-yl)-6-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (3b): ^{1}H NMR δ (ppm) 8.32 (s, 1H, C5-H) and 7.21-7.62 ppm (m, 13H, Ar-H); ^{13}C NMR : δ 161.17, 139.04, 137.11, 136.23, 134.24, 132.06, 131.55, 129.22, 128.55, 128.44, 127.39, 126.95, 126.14, 125.88, 125.02, 124.58, 123.44, 122.34.

2-(Biphenyl-4-yl)-6-(4-fluorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (3c): ^{1}H NMR δ 8.52 (ppm) (s, 1H, C5-H) and 7.30-7.64 ppm (m, 13H, Ar-H). ^{13}C NMR: 116.11, 123.13, 127.44, 127.24, 128.12, 128.76, 129.12, 133.04, 136.22, 140.02, 141.02, 143.52.

2-(Biphenyl-4-yl)-6-(2,4-dichlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (3d): ^{1}H NMR δ (ppm) 8.53 (s, 1H, C5-H) and 7.28-8.17 ppm (m, 12H, Ar-H). ^{13}C NMR : 121.2, 126.12, 127.23, 127.35, 127.94, 128.11, 129.32, 130.44, 131.44, 133.55, 133.95, 135.32, 137.12, 140.23, 141.2, 143.7.

2-(Biphenyl-4-yl)-6-(4-bromophenyl)imidazo[2,1-b][1,3,4]thiadiazole (3e): ; ^{1}H NMR δ (ppm) 8.24 (s, 1H, C_5-H) and 7.12-7.92 ppm (m, 13H, Ar-H). ^{13}C NMR: 122.6, 123.42, 127.56, 127.95,128.1, 128.21, 128.43, 129.11, 132.21,133.04, 136.12, 140.24, 140.9, 143.44.

2-(3-Fluorobiphenyl-4-yl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole (3f): ^{1}H NMR δ (ppm) 8.58 (s, 1H, C_5-H) and 7.25-8.14 ppm (m, 13H, Ar-H); ^{13}C NMR: 113.5,119.22,120.65,122.74,126.23,127.01,127.23,127.85,129.02,131.22,131.89,133.32,137.45,140.81, 142.12, 149.23,165.95.



Scheme 1. One-pot synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazole.

RESULTS AND DISCUSSION:

Biphenylimidazo[2,1-b][1,3,4]thiadiazole is one of the valuable heterocycles in the medicinal chemistry which was synthesized by refluxing of 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine and α-bromo ketones in ethanol, PEG and ionic liquids. The main drawback associated with this method was longer reaction time and poor yield and use of unstable and lachrymatric α-halo ketones and poisonous catalyst and solvents. Considering the adverse effect of α-halo ketones and volatile organic solvents prompted our interest to design new method with high atom economy, excellent yield and rapid reaction for the synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazole. Ultrasound wave used to enhance reaction rate and α--tosyloxyketones were condense with 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine to obtained biphenylimidazo[2,1-b][1,3,4]thiadiazole. Initially, reactions were carried out in different solvents such as water, ethanol, propan-ol, DMF, glycerol etc. It was observed that, when we used glycerol as a solvent it was found that the rate and yield of the products increase under ultrasound irradiation (Table 1). Same reaction was carried out in glycerol and water it again increases the yield of the reaction. Glycerol and water are best choice of solvents for the further reactions. To generalize the scope this method various α--tosyloxyketones were used to synthesized corresponding biphenylimidazo[2,1-b][1,3,4]thiadiazoles (Table 2).

Table 1. Optimization of reaction medium

Solvent	Temp. (°C)	Time[a](min.)	Yield %[b]
Water	85	-	No reaction
Ethanol	85	37	75
Propan-2-ol	85	32	64-68
DMF	85	35-36	62-68
glycerol	85	25-30	85-87
Glycerol+Water	**85**	**11-12**	**94-98**

[a] isolated yield; [b] Time for overall reaction.

Table 2 Evaluation of compounds **(4a-4j)[a]**

Product	R	Time min.	Temp. (^{O}C)	YIELD[a] %	M.P(^{O}C) found	M.P(^{O}C) reported
4a	H	12	85	95	262	263
4b	4-Cl	11	80	97	273-274	272-274
4c	4-F	11	80	98	262-264	261-263
4d	2,4-Di-Chloro	11	80	98	256-259	251-258
4e	4-Br	12	85	95	254-256	254-256
4f	H	14	85	94	241	242

[a]Reaction condition:1) 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine (0.002 mol),2) acetophenones (0.002 mol), 3) NBS(0.002mol); (Glycerol-water). m.p. melting point; [a]isolated yield.

CONCLUSION:

Designed an expeditious one pot, green method for the synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazoles from the coupling of α--tosyloxyketones and 5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine under ultrasound in the presence of glycerol-water as a green medium. Use of non-volatile, inexpensive and radially available green solvent, metal and catalysts free,

excellent yields with high purity of the products (94-98%) are the important advantages of this method.

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