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ARTICLE

Ultrasound Assisted New Imines of 3*E*-3-(4-Substituted benzylidene)-4-(substituted-1,3,4-thiadiazole-2-ylimino)pentane-2-one and their Antimicrobial Studies

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ABSTRACT

A new series of Schiff bases of 3-(4-substituted benzylidene)-4-(substituted-1,3,4-thiadiazole-2-ylimino)pentane-2-one having various substituents of aryl attached to acetoacetone by Knovengel condensation and substituted 1,3,4-thiadiazole were synthesized by using solid supported tetrabutylammonium hydrogen sulfate in microwave irradiation. The synthesized Schiff bases have been evaluated by ^{1}H NMR, elemental analysis, FTIR, mass spectroscopy. All Schiff bases have been screened for their antimicrobial activities. These compounds possess good result of antimicrobial studies.

KEYWORDS

Schiff base, Acetoacetone, Thiadiazole, Ultrasound.

INTRODUCTION

Heterocyclic compounds play an important role in various medicinal therapies such as cancer therapy [1]. This is due to presence of effective conjugation in the ring and presence of donating substituent at proper position. The derivative of thiazolidine-2,4-dione and 1,3,4-thiadiazoles are found to have good antimicrobial activities. Biologists are interested to synthesize variety of 1,3,4-thiadazoies and thiazolidine-2,4-dione derivatives in recent era as these compound has wide range of biological activities [2,3]. After closely examined by various reviews on the mechanism and activities of these compounds, they are used as drugs like antidiabetic, anti-inflammatory, antifungal, antibacterial [4,5], *etc*.

In present work, efforts have been taken to synthesis 3-(4-substituted benzylidene)-4-(substituted-1,3,4-thiadiazole-2-ylimino)pentane-2-one in one step instead of two steps along with solid supported tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst [4,6]. The aim of present work is to synthesize novel Schiff bases under ultra sound method from substituted aromatic aldehydes, acetoacetone and 2-amino-(5-substituted aryl)-1,3,4-thiadazole. The obtained Schiff bases acts as bi and tridentate ligand for synthesize of complex from various metal ions. The synthesized Schiff bases and their metal complexes will be evaluated by physico-chemical techniques and also screened by antimicrobial activities [7,8]. Synthesized Schiff base ligands were tested by various analytical techniques

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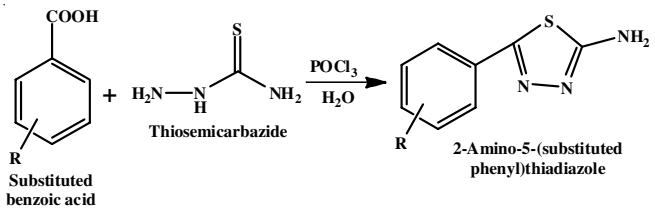
to elucidate their molecular structure [3] and also screened with biological activity.

EXPERIMENTAL

All the reagents and starting materials (AR Grade) were commercially purchased and used without purification except 1,3,4-thiadiazole, which is to be prepared by reported method in the laboratory and purified by obeying all protocols. The melting point was recorded on Cotech digital melting point apparatus. Elemental C, H, N and S analysis was carried out on a Fison EA1108 analyzer. The infrared (FTIR) spectra were recorded by using FITR 8300 Shimadzu spectrometer by using CsI disk in the frequency range of 4000 to 400 cm^{-1}. The ^1H NMR spectra were recorded on Brunker 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. Mass spectra were recorded by mass wiff (turbo spray) spectrometer. The progress of reaction was monitored by using silica plates, petroleum ether, ethyl acetate (7:3 v/v) and benzene acetone (7:3 v/v) as the solvent system. All synthesized compounds were good yield (80-90%) with confirm the strength of adopted procedure.

Synthesis of 2-amino-5-(substituted phenyl)thiadiazole: A round bottom flask charged with a mixture of substituted benzoic acid (10 mmol), thiosemicarbazide (10 mmol) and phosphorous oxychloride (3 mL) was reflux under 80 ºC for 1 h. The solution becomes liquid and fumes of HCl are formed then add 45 mL ice cold distilled water drop wise till the fumes stops then further reflux the mixture for 2 h then neutralized the mixture by 40% KOH solution, the precipitate formed was recrystallized in methanol and completion of reaction are monitored by thin layer chromatography (TLC) (**Scheme-I**).



Scheme-I

Synthesis of novel Schiff base 3-substituted benzylidene-4(5-substituted aryl-[1,3,4]-thiadiazole-2-ylimino)pentan-2-one: A mixture of substituted aromatic aldehyde, acetoacetone (10 mmol) each and along with 10 mol % solid supported tetra butylammonium hydrogen sulphate (TBAHS) [9] in methanol (20 mL) are irradiated with ultrasound waves at 70 ºC by dipping probe in to a solution for 2 h. The progress of reaction was monitored by using pet ether and ethyl acetate system (7:3 v/v). After that 2-amino-5-(substituted aryl)-thiadiazole (10 mmol) added and continued irradiation of ultra sound waves for 1 h. The progress of reaction was monitored by benzene, acetone system (7:3 v/v) and solution was poured on flaks of ice (**Scheme-II**). The obtained solid yellow precipitate was filtered, dried and recrystallized in methanol [10,11].

RESULTS AND DISCUSSION

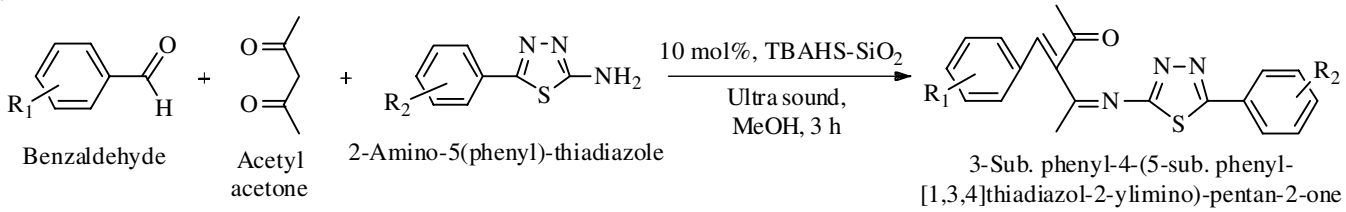
A mixture of substituted aldehyde (10 mmol), acetoacetone (10 mmol) along with 10 mol % solid supported tetrabutylamine hydrogen sulphate (TBAHS) in methanol (20 mL) were irradiated with ultra sound waves for 4 h for completion of reaction. Then in same reaction mixture 2-amino-5-(substituted phenyl)thiadiazole (10 mmol) added and continued irradiation of ultrasound waves for 3 h. The progress of reaction was monitored by TLC using benzene and acetone solvent system (7:3 v/v). After completion of reaction the reaction mixture poured on ice flakes a yellow colour solid obtained which is expected Schiff base was filtered, washed and recrystallized in methanol [11,12].

3-(Furan-2-yl methylene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 82%, m.p.: 107 ºC, IR (KBr, ν_{max}, cm^{-1}): 1708 (C=O), 1633 (C=N), 1020 (N-N), 634 (C-S-C), ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H, N=C-CH_3), 2.10 (s, 3H, O=C-CH_3), 5.30 (s, 1H, HC=C), 2.41 (s, 3H, Ar-CH_3), 6.20-7.80 (m, 8H, Ar-H). Turbo spray MS-*m/z* 351 $(M+1)^+$. Anal. for $C_{19}H_{17}N_3O_2S$ (%): C, 65.00; H, 4.88; N, 11.97; S, 9.13; O, 9.12.

(3*E*)-3-(4-Fluorobenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 80%, m.p.: 145 ºC, IR (KBr, ν_{max}, cm^{-1}): 1693 (C=O), 1620 (C=N), 1018 (N-N), 632 (C-S-C), ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (S, 3H, N=C-CH_3), 2.25 (s, 3H, O=C-CH_3), 5.50 (s, 1H, HC=C), 6.30-8.35 (m, 8H, Ar-H). Turbo spray MS *m/z* 379 $(M+1)^+$. Anal. for $C_{21}H_{18}N_3OSF$ (%): C, 66.55; H, 5.05; N, 11.09; S, 8.46; O, 8.44.

(3*E*)-3-(4-Methoxybenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 85%, m.p.: 136 ºC, IR (KBr, ν_{max}, cm^{-1}): 1693 (C=O), 1606 (C=N), 1033 (N-N), 634 (C-S-C), ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (s, 3H, N=C-CH_3), 2.15 (s, 3H, O=C-CH_3), 5.36 (s, 1H, HC=C), 6.89-7.79 (m, 8H, Ar-H). Turbo spray MS *m/z* 391 $(M+1)^+$. Anal. for $C_{22}H_{21}N_3O_2S$ (%): C, 67.40; H, 5.05; N, 10.71; S, 8.17; O, 12.23.

(3*E*)-3-(4-Nitrobenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 81%, m.p.: 138 °C, IR (KBr, ν_{max}, cm^{-1}): 1726 (C=O), 1662 (C=N), 1012 (N-N), 603 (C-S-C), ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (S, 3H, N=C-CH_3), 2.19 (S, 3H, O=C-CH_3), 5.55 (S, 1H, HC=C), 7.35-8.23 (M, 8H, Ar-H),Turbo spray MS *m/z* 406 $(M+1)^+$. Anal. for $C_{21}H_{18}N_4O_3S$ (%): C, 62.12; H, 4.72; N, 13.80; S, 7.89; O, 15.75.



Scheme-II

TABLE-1
PRILIMINARY *in vitro* ANTIBACTERIAL AND ANTIFUNGAL SCREENING ACTIVITIE OF LIGANDS

Compounds	Inhibition zone (mm)															
	Fungal activity								Bacterial activity							
	A. nigar		*C. albicans*		*Crysogenun*		*Rhizopus*		*S. antius*		*Shegolla*		*E. coli*		*B. megaterium*	
µg/mL	100	200	100	200	100	200	100	200	100	200	100	200	100	200	100	200
$C_{19}H_{17}N_3O_2S$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
$C_{21}H_{18}N_3OSF$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
$C_{22}H_{21}N_3O_2S$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
$C_{21}H_{18}N_4O_3S$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	++
$C_{21}H_{19}N_3O_2S$	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
$C_{21}H_{18}N_3OSCl$	++	+++	++	+++	++	++	++	++	++	++	++	++	++	++	++	+++
$C_{22}H_{21}N_3OS$	+	++	+	++	+	+	+	+	+	+	+	+	+	+	+	++
$C_{22}H_{21}N_3O_3S$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ = 5-10 mm, ++ = 11-20 mm, +++ = larger than 20 mm and – = no inhibition.

(3*E*)-3-(4-Hydroxybenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 86%, m.p.: 132 ºC, IR (KBr, ν_{max}, cm^{-1}): 1704 (C=O), 1635 (C=N), 1062 (N-N), 634 (C-S-C), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H, N=C-CH_3), 2.19 (s, 3H, O=C-CH_3), 5.55 (s, 1H, HC=C), 7.35-8.23 (m, 8H, Ar-H). Turbo spray MS *m/z* 381 $(M+1)^+$, Anal. for $C_{21}H_{19}N_3O_2S$ (%): C, 66.20; H, 5.29; N, 11.02; S, 8.41; O, 12.59.

(3*E*)-3-(4-Chlorobenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 78%, m.p.: 142 ºC, IR (KBr, ν_{max}, cm^{-1}): 1707 (C=O), 1660 (C=N), 1012 (N-N), 632 (C-S-C), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H, N=C-CH_3), 2.22 (s, 3H, O=C-CH_3), 5.45 (s, 1H, HC=C), 7.33-8.33 (m, 8H, Ar-H). Turbo spray MS-*m/z* 395 $(M+1)^+$. Anal. for $C_{21}H_{18}N_3OSCl$ (%): C, 63.85; H, 4.85; N, 10.63; S, 8.11; O, 8.10.

(3*E*)-3-(4-Methylbenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 79%, m.p.: 139 ºC, IR (KBr, ν_{max}, cm^{-1}): 1707 (C=O), 1656 (C=N), 1022 (N-N), 634 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H, N=C-CH_3), 2.17 (s, 3H, O=C-CH_3), 5.35 (s, 1H, HC=C), 6.90-7.85 (m, 8H, Ar-H). Turbo spray MS-*m/z* 375 $(M+1)^+$. Anal. for $C_{22}H_{21}N_3OS$ (%): C, 70.46; H, 5.91; N, 11.20; S, 8.55; O, 8.53.

(3*E*)-3-(4-Hydroxy-3-methoxybenzylidene)-4-(5-*p*-tolyl-1,3,4-thiadiazole-2-ylimino)pentane-2-one: Yield: 87%, m.p.: 144 ºC, IR (KBr, ν_{max}, cm^{-1}): 1691 (C=O), 1633 (C=N), 1033 (N-N), 634 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H, N=C-CH_3), 2.22 (s, 3H, O=C-CH_3), 5.45 (s, 1H, HC=C), 6.82-7.79 (M, 8H, Ar-H). Turbo spray MS *m/z* 407 $(M+1)^+$. Anal. for $C_{22}H_{21}N_3O_3S$ (%): C, 64.92; H, 5.45; N, 10.32; S, 7.88; O, 15.72.

Antimicrobial activity: The *in vitro* antifungal and antimicrobial activities [13] of synthesized Schiff bases have been studied by disc diffusion method. The antifungal and antimicrobial activities were done at 100 µg/mL concentration in chloroform solvent using four fungal and bacterial strains. *Aspergillus niger*, *Candida albicans*, *Chrysogenum*, *Rhizopus* and *Shigella*, *Staphylococcus aureus*, *Escherichia coli, Bacillus megaterium* by minimum inhibitory concentration method (MIC). These fungal and bacterial strains were incubated for 24 h at 28 ºC. Standard fluconazole and streptomycin drugs were used for comparison under similar condition. Activity was determined by measuring the diameter of the zone of inhibition (mm). It was observed that $C_{21}H_{19}N_3O_2S$ and $C_{21}H_{18}N_3OSCl$ ligands are more active against the fungal and bacterial strains *Aspergillus niger* and *Staphylococcus aureus* as compare to other fungal and bacterial strains (Table-1). Other ligands were moderately active against all fungal and bacterial strains [14].

Conclusion

The synthesis of novel Schiff bases with substituted 1,3,4-thiadiazole, substituted aryls and acetoacetone by the condensation in presence of solid supported tetrabutylammonium hydrogen sulfate (TBAHS) catalyst with ultrasound method is reported. The synthesized products were evaluated analytically and spectroscopically. There are number of advantages of selected catalytic and ultrasound method like high yield, decreased time and excellent selectivity of condensation. All the synthesized Schiff bases were also screened by antimicrobial activities and found to be moderate to high antifungal and antibacterial activity with respect to standard.

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