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Trimethylsilyl Chloride Catalyzed Highly Efficient Synthesis of Schiff Bases of Thiazole in Glycerol under Microwave Irradiation

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ABSTRACT

A green and environmentally benign protocol is developed for the synthesis of Schiff bases of sulphur containing compound by irradiating thiazole and pyrazole aldehyde in glycerol under microwave irradiation at 70 ºC with trimethylsilyl chloride (TMSCl) as a catalyst. The method has advantages such as excellent yield, use of green solvent, easy work-up and most important the reaction completed within 2.5 min by using TMSCl catalyst. The TMSCl is an acidic catalyst, which enhances the yield of product, reaction time (with microwave, with reflux at 75 ºC and with stirring at room temperature) which can be easily removed from reaction mask.

KEYWORDS

Trimethylsilyl chloride, Pyrazole aldehyde, 2-Aminothaizole, Schiff bases, Glycerol.

INTRODUCTION

The compounds containing nitrogen, sulphur or oxygen as a heteroatom showing high degree of biological and pharmaceutical activity. Particularly, heterocyclic molecules containing thiazole, pyrazole, amid, azetidine and triazole moieties exhibit wide range of biological activities. Thaizoles are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process. 4-Phenyl-2-aminothiazole gives us a wide range of biological, pharmacological and medicinal applications like antifungal [1], antibacterial [2], antihypertensive [3], anti-HIV [4], anti-inflammation [5], antihelmintic and possesses immune suppressant [6], pesticide activities [7], *etc*. 2-Aminothiazole nucleus is a potential pharmacophore for a broad spectrum of activities, comprising of antibacterial [8]. Moreover organic compounds containing thiazole nucleus are found to possess high second order hyper polarizability [9-12]. The pyrazole and its derivatives were also possess antioxidant [13,14], anti-inflammatory [15-18], antimicrobial [19-21], antimalarial [22], *etc*.

The modifications of Schiff bases derived from differently substituted heterocyclic compounds have proven highly effective with improved potency and lesser toxicity. Microwave assisted synthesis has become very important tool in organic synthesis especially for heterocyclic compounds, due to very simple,

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atom economy, convenient and easy work-up procedure [23]. Glycerol acts as a green reaction media as it is "organic water" because of easily form strong hydrogen-bond networks, polar, biodegradable, easily available, cheap, and non-toxic. Glycerol and PEG have a wide range of solubility for organic and inorganic compounds, including transition metal catalysts [24-29]. Trimethylsilyl chloride (TMSCl) reacts with alcohols, carboxylic acids, which is probably the ultimate catalyst for acid catalysed reactions [30,31]. Herein, we wish to report an efficient microwave-assisted synthesis of Schiff bases of thiazole and pyrazole carbaldehyde in lesser time with excellent yields.

EXPERIMENTAL

Preparation of substituted 1,3-diphenyl-4-pyrazol (methylene)-2-aminothiazole (3a-i): 2-Aminothiazole (0.01 mol) is mixed with pyrazole carbaldehyde (0.01 mol) in glycerol by introducing catalytical amount of TMSCl and , irradiate with 400 W under microwave irradiation at 70 ºC which resulted in the completion of the reaction within 2.5 min. Then reaction product poured on crush ice, filtered and dried (**Scheme-I**). The spectral data were consistent with previous literature reports [26].

4-(4-Chlorophenyl)-*N*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazol-2-amine (3b): m.p.: 257-259 ºC (Lit. 259-261 ºC) [26]. IR (KBr, ν_{max}, cm^{-1}): 1628 (C=N), 859(C-Cl). ^{1}H NMR (400 MHz) δ ppm: 9.9 (s, 1H), 8.5 (s, 1H), 7.1 (s, 1H), 6.9-7.7 (m, 14H). ES-MS (*m/z*): 439 [M+H]; HRMS-EI: found: 68.89; calculated: C, 69.00.

4-(4-Bromophenyl)-*N*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazol-2-amine (3c): m.p.: 252-254 ºC (Lit. 254-255 ºC) [26]. IR (KBr, ν_{max}, cm^{-1}): 1623 (C=N), 762 (C-Br). ES-MS (*m/z*): 481 [M+H]; HRMS-EI: found: 60.95; calculated: C, 60.85.

4-(4-Chlorophenyl)-N-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazol-2-amine (3f): m.p.: 94-96 ºC (Lit. 93-95 ºC) [26]. IR (KBr, ν_{max}, cm^{-1}): 1619 (C=N), 769 (Cl). ^{1}H NMR (400 MHz) δ ppm: 9.8 (s, 1H), 8.3 (s, 1H), 6.9 (s, 1H), 7.0-7.9 (m, 13H).

4-(4-Nitrophenyl)-*N*-((1,3-diphenyl-1*H*-pyrazol-4-yl)-methylene)thiazol-2-amine (3g): m.p.: 257-259 ºC (Lit. 251-253 ºC) [26]. IR (KBr, ν_{max}, cm^{-1}): 1618 (C=N), 1460 (NO_2). ^{1}H NMR (400 MHz) δ ppm: 9.98 (s, 1H), 8.7 (s, 1H), 7.08 (s, 1H), 6.6-8.4 (m, 14H).

4-(4-Chlorophenyl)-*N*-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazol-2-amine (3k): m.p.: 125-127 ºC. IR (KBr, ν_{max}, cm^{-1}): 9.8 (s, 1H), 8.3 (s, 1H), 7.2 (s, 1H), 6.8-7.8 (m, 13H).

RESULTS AND DISCUSSION

The Schiff bases of 2-aminothiazole and pyrazolyl aldehyde derivatives have vert much attracted because of their wide applications in the field of pharmaceuticals as it contained the both biologically and pharmacologically important group *i.e.* thiazole and pyrazole rings. The wide range of methods are there for the synthesis of Schiff bases, but most of them used unstable, volatile, harmful, hazardous organic solvents and also longer reaction time. To optimize the reaction conditions, initially, we have performed the series of reactions with various solvent and found that reaction proceed in organic solvent for long time duration. In absence of catalyst, the reaction did not proceed. After screening of different solvent, glycerol with TMSCl catalyst was found to be best reaction condition (Table-1, entry 6).

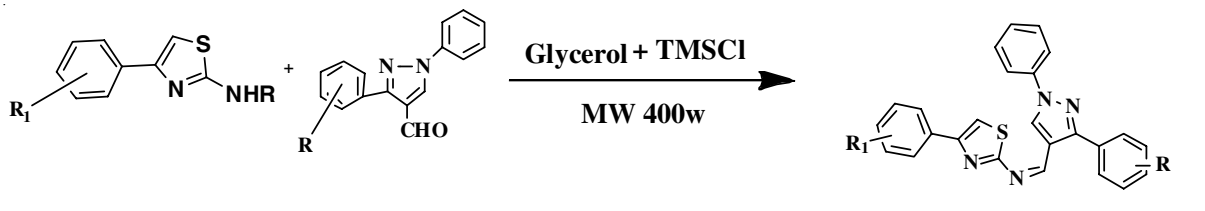
TABLE-1
OPTIMIZATION OF THE SOLVENT FOR THE SYNTHESIS OF SCHIFF BASES (**3a**)

Entry	Solvents	Volume (mL)	Time (min)	Yield (%)[a]
1	Toluene	5	30	55-60
2	Dichloromethane	5	25	58-63
3	1,4-dioxane	5	23	60-65
5	Isopropyl alcohol	5	18	73-78
6	Glycerol	5	13	82-87

[a]Isolated yield product **3a**

The IR spectra of compound **3b** shows prominent peaks at 1622 cm^{-1} for Schiff base conformation C=N, 861 cm^{-1} for C-Cl of 4-chloroaryl-2aminothiazole and their absence of the stretching at band for -NH and C=O. ^{1}H NMR of compound **3b** shows characteristic singlet at δ ppm 7.1 for 1H of H-C=N it is conjugation with pyrazole ring, δ ppm 8.5 shows singlet for 1H of pyrazole ring, δ ppm 9.9 as a singlet which is the aromatic ring proton nearest to nitrogen (thiazole ring proton). The above spectral data confirmed the structure of the product 3b. All the above spectral data clearly shows the formation of title compounds.

Further, we screened different catalysts such as acetic acid, conc. HCl, LiCl and TMSCl in the synthesis of these compounds. It is found that the catalyst like acetic acid, conc. HCl and LiCl gave moderate yield of compound **3a** and firstly required higher reaction time However, TMSCl gave excellent yield of compound **3a** in shorter reaction time as compared to other catalysts (Table-2, entry 4).



1 **2** **3a-k**

(*Z*)-4-phenyl-*N*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazol-2-amine

Scheme-I: Synthesis of Schiff bases of pyrazolyl carbaldehyde and 2-amino thiazole

TABLE-2
OPTIMIZATION OF THE CATALYST FOR THE SYNTHESIS OF SCHIFF BASES (**3a**)[a]

Entry	Catalyst	Time (min)	Yield (%)[b]
1	Acetic acid	13	84
2	Conc. HCl	12	86
3	LiCl	10	87
4	TMSCl	5	94

[a]Reaction conditions: Pyrazole aldehyde (1 mmol), 2-aminothiazole (1 mmol), catalyst (3-4 drops), glycerol 5 mL, microwave irradiation at 400 W and 70 °C; [b]Isolated yield.

The effect of temperature on the reaction were also evaluated at room temperature, 40º, 50º and 70 ºC. The best results were obtained at 70 ºC (Table-3, entry 4). It is found that TMSCl catalyst completed this reaction within 15 min with refluxed at 75 ºC while other catalysts required 40 to 80 min. However, at room temperature, the reaction with constant stirring using TMSCl yields the excellent results in 50-60 min whereas other catalysts take more time 150 to 180 min for the completion of the reaction.

TABLE-3
OPTIMIZATION OF THE TEMPERATURE FOR THE SYNTHESIS OF SCHIFF BASES (**3a**)

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	Room temperature	40	70
2	40	35	72
3	50	25	80
4	70	5	94

[a]Isolated yield

These results were encourage us to investigate the scope of reaction and to generalize the scope reaction of this new method under optimized conditions. As shown in Table-4, a series of pyrazole carbaldehyde successfully reacted with series 2-aminothiazoles in glycerol at 70 ºC under microwave irradiator with excellent yields.

TABLE-4
EVALUATION OF COMPOUNDS (**3a-i**)

Compd.	R	R_1	Yield (%)	Reaction time (min)
3a	H	H	85	2.1-2.3
3b	Cl	H	86	1.9-2.1
3c	Br	H	86	1.9-2.1
3d	CH_3	H	87	1.9-2.1
3e	Br	Cl	88	1.9-2.1
3f	Cl	Cl	87	1.9-2.1
3g	NO_2	Cl	89	1.9-2.1
3h	NO_2	H	90	1.9-2.1
3i	CH_3	Cl	89	1.9-2.1
3j	Cl	NO_2	90	1.9-2.1
3k	Cl	F	88	2.0-2.4

Conclusion

A prospective alternative protocol for the synthesis of Schiff bases containing thiazole and pyrazole aldehyde moeity is described. This protocol has important advantages over previously reported procedures like lesser reaction time, eco-friendly nature and simple work-up method.

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