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An expeditious synthetic approach towards the synthesis of *Bis*-Schiff bases (aldazines) using ultrasound

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ABSTRACT

Aldazines (*Bis*-Schiff bases) **1**–**24** were synthesized using aromatic aldehydes (heterocyclic and benzaldehydes) and hydrazine hydrate under reflux using conventional heating and/or *via* ultrasound irradiation using $BiCl_3$ as catalyst. Ultrasonication conditions with cat. $BiCl_3$ proved to be an effective, environmentally friendly synthetic procedure. This methodology is robust in the presence of electron donating and electron withdrawing groups affording desired products with high yields (>95%) in just a couple of minutes vs. hours using conventional heating.

1. Introduction

Schiff bases are an important class of compounds in organic chemistry exhibiting in many cases biological and pharmacological activities [1–5]. Several Schiff bases, some containing different heterocyclic moieties, have been reported to exhibit anticancer [6], antibacterial [7], antifungal [8,9], herbicidal [10], cytotoxic [11], anticonvulsant [12], and antiproliferative [13] activities. Complexes also containing Schiff bases have also been found to posses antibacterial [14–20], antifungal [21,22], anticancer [23,24], and herbicidal effects [25]. Aldazines or *Bis*-Schiff bases have received great attention because of their analytical applications, particularly as good spectrophotometric [26] and flourimetric agents [27,28].

Although several synthetic methods for the synthesis of Schiff and *Bis*-Schiff bases have been reported [29–38], many of them suffer of several disadvantages such as low yields, prolonged reaction times, harsh reaction conditions, and requiring excess amounts of catalysts. Therefore, there is a need to identify new, efficient, economical synthetic methods for this class of compounds.

The chemical application of ultrasound irradiation, also referred to as sonochemistry, has become a leading methodology and important tool in the field of synthetic organic chemistry. The use of ultrasound irradiation to drive and expedite chemical transformations has made and continues to make a great impact in organic synthesis, a fact well documented in the literature [39,40].

In past few decades bismuth compounds have been used as catalyst in organic synthesis. Their low cost, high stability and ease of handling make them both attractive and useful catalysts for synthetic applications. Among them bismuth(III) trichloride ($BiCl_3$) has been reported to be an efficient catalyst for many widely used organic transformations, such as intramolecular hetero-Diels–Alder reactions [41], selective hydroarylation of styrenes [42], *C*-alkylation of pyrroles [43], regioselective ring opening of epoxides [44], and quinoline synthesis [45].

Although several Schiff bases have been synthesized via sonication irradiation using catalysts, to the best of our knowledge no study has been reported on the synthesis of *Bis*-Schiff bases with the assistance of ultrasound irradiation using $BiCl_3$ as catalyst.

We herein wish to report a newly developed method for the quick and high-yielding synthesis of aldazines (*Bis*-Schiff bases) using ultrasound irradiation in the presence of catalytic amounts of bismuth(III) trichloride. A comparison of this novel ultrasound-based synthetic approach with conventional synthetic methods demonstrates that our new methodology is robust and

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compatible with electron donating and electron withdrawing groups affording desired products with high yields (>95%) in just a couple of minutes vs. hours when using conventional heating.

2. Result and discussion

2.1. Chemistry

Bis-Schiff bases **1–24** were synthesized by sonication as well as conventional heating methods (Table 1).

In the conventional heating study, benzaldehyde was dissolved in absolute ethanol followed by the addition of 2–3 drops of conc. hydrochloric acid, and hydrazine hydrate. The reaction mixture was heated to reflux for 2–4 h, the solvent evaporated, and the resulting residue washed with and recrystallized from ethanol to afford desired product with 70–80% yield. When the same reaction was repeated using $BiCl_3$ as a catalyst instead of hydrochloric acid no significant yield improvement and time shortening were observed. However, when the same reaction was carried out in the presence of ultrasound irradiation at room temperature (instead of conventional heating) it was found that a precipitate was formed within 2 min. This solid was filtered, collected, and washed with water and proved to be desired pure product with 95% yield conversion. Only when necessary the final product had to be purified *via* recrystallization from ethanol (Scheme 1). The identity and structure of the *Bis*-Schiff bases (**1–24**) were confirmed by ^{1}H NMR, mass spectrum, and elemental analyses.

Table 1
Comparison of conventional (Convn.) vs. ultrasonication (US) method.

S. No.	Aldehyde derivatives	Conventional time (min)	Ultrasonication time (min)	Yield % (Convn.)	Yield % (US)
1	2-Methoxy benzaldehyde	60	1	68	>95
2	4-Methoxy benzaldehyde	60	1	75	>95
3	4,5-Dimethoxy benzaldehyde	60	1	75	>95
4	3,4,5-Trimethoxy benzaldehyde	60	1	66	>95
5	2-Ethoxy benzaldehyde	60	1	82	>95
6	4-Ethoxy benzaldehyde	60	1	76	>95
7	2-Chloro benzaldehyde	60	1	80	>95
8	3-Chloro benzaldehyde	60	1	68	>95
9	4-Chloro benzaldehyde	60	1	78	>95
10	3,4-Dichloro benzaldehyde	120	1	76	>95
11	2,4-Dichloro benzaldehyde	120	1	66	>95
12	2-Fluoro benzaldehyde	120	2	67	>95
13	3-Fluoro benzaldehyde	120	2	78	>95
14	2-Furfural	60	1	66	>95
15	3-Thiophene aldehyde	60	1	68	>95
16	2-Nitro benzaldehyde	120	2	78	>95
17	3-Nitro benzaldehyde	120	2	80	>95
18	2-Napthaldehyde	60	2	66	>95
19	4-Methylthio benzaldehyde	60	1	75	>95
20	4-*N*,*N*-Dimethylamino benzaldehyde	60	1	77	>95
21	Benzaldehyde	60	1	70	>95
22	2-Hydroxy benzaldehyde	120	1	78	>95
23	2-Methyl benzaldehyde	60	1	76	>95
24	4-Methyl benzaldehyde	60	1	68	>95

The conventional heating method was found to be time consuming suffering of low yields when compared to our ultrasonication-based method (Table 1). The role of $BiCl_3$ in our ultrasonication-based method was found to accelerate the reaction further. This was confirmed by carrying out a reaction in the absence of $BiCl_3$ finding that, although the reaction took place, it took longer (10–15 min) vs. the 1–2 min when in the presence of $BiCl_3$.

We confirmed the robustness of our $BiCl_3$-catalyzed ultrasonication-based method using heterocyclic aldehydes obtaining desired *Bis*-Schiff bases **14** and **15** in excellent yields. We also assessed that our method is compatible with a broad range of electron donating and electron withdrawing groups present in the benzaldehyde moiety. Moreover, the final crude products were isolated in many cases highly pure, and only when necessary they were recrystallized from ethanol.

3. Experimental details

NMR spectra were recorded on a Bruker AM 300 MHz instrument, Bruker Avance-300, France. A Carlo Erba Strumentazion-Mod-1106, Italy was used for CHN analysis. Mass Spectra were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was carried out on pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany). UV light (254 nm and 365 nm) and/or iodine was used to visualize/develop the TLC plates.

3.1. Ultrasonic process equipment

Ultrasonic mediated reactions were carried out in Clifton Ultrasonic Bath (2 x T2A, 300 W, DU-4) made by Nickel Electro Ltd, Weston-S-Mare Somerset, England. All the experimental parameters were performed with output power of 300 W.

3.2. General procedure for the synthesis of compounds

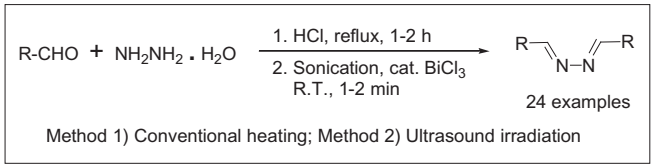
3.2.1. Conventional method

To a solution of benzaldehyde (1 mmol) in ethanol (10 mL) was added conc. HCl (1–2 drops) and then hydrazine hydrate 55% (Sigma Alrich) (1 mL). The reaction was stirred and refluxed for a specific time (see Table 1). Upon reaction completion (TLC analysis) the solvent was evaporated, the resulting residue washed with cold water, and then re-crystallized from ethanol to afford desired product.

3.2.2. Ultrasonication method

A reaction flask containing benzaldehyde (1 mmol), hydrazine hydrate 55% (Sigma Alrich) (1 mL) and catalytic (0.1 mol%) amounts of $BiCl_3$ was immersed in an ultrasonic bath containing water at room temperature. The reaction mixture was exposed to ultrasound irradiation for 1–2 min (reaction complete based on TLC analysis). The resulting precipitate is filtered and washed with water to afford pure desired product (yellow crystals). Only, when necessary, final products were re-crystallized from ethanol.

*3.2.2.1. 2-Methoxybenzaldehyde-N-[-(2-methoxyphenyl)methylidene] hydrazone (**1**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.02 (s, 1H, –N=CH), 7.97, (dd, 1H, $J_{6,4}$ = 1.5 $J_{6,5}$ = 7.2 Hz, H-6), 7.58 (m, 2H, H-5), 7.12, (d, 1H, $J_{3,4}$ = 8.4 Hz, H-3), 7.05, (t, 2H, $J_{4,(5,6)}$ = 7.5 Hz, H-4; EI MS: *m*/*z* (rel. abund.%), 268 (M^+, 26), 237 (100), 150 (64),



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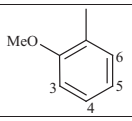
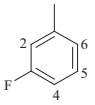
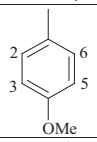
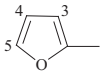
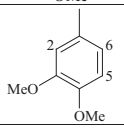
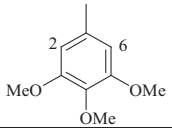
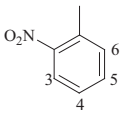
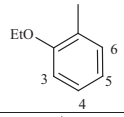
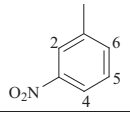
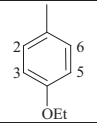
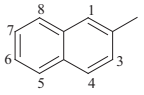
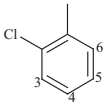
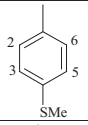
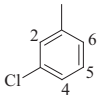
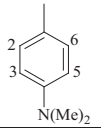
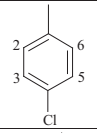
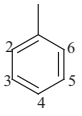
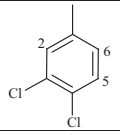
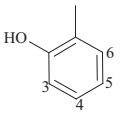
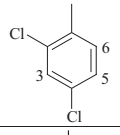
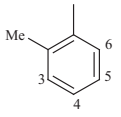
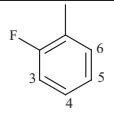
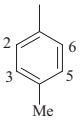
1		13	
2		14	
3		15	
4		16	
5		17	
6		18	
7		19	
8		20	
9		21	
10		22	
11		23	
12		24	

Scheme 1. Synthesis of *Bis*-Schiff bases (**1**–**24**).

119 (100), 91 (68), 77 (30). Anal. Calcd for $C_{16}H_{16}N_2O_2$, C = 71.62, H = 6.02, N = 10.44. Found: C = 71.59, H = 6.01, N = 10.42.

*3.2.2.2. 4-Methoxybenzaldehyde-N-[-(4-methoxyphenyl)methylidene] hydrazone (**2**).* Yield 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.57 (s, 1H, –N=CH), 7.83, (d, 2H, $J_{6,5/2,3}$ = 8.7 Hz, H-6/2), 7.02 (d, 2H, $J_{5,6/3,2}$ = 8.7 Hz, H-3/5), 1.41(s, 6H, CH_3); EI MS: *m*/*z* (rel. abund.%), 268 (M^+, 87), 241 (15), 147 (100), 77 (20). Anal. Calcd for $C_{16}H_{16}N_2O_2$, C = 71.62, H = 6.02, N = 10.44. Found: C = 71.58, H = 6.02, N = 10.40.

*3.2.2.3. 3,4-Dimethoxybenzaldehyde-N-[-(3,4-dimethoxyphenyl)methylidene] hydrazone (**3**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.57 (s, 2H, –N=CH), 7.72 (d, 2H, $J_{6,5}$ = 7.06 Hz, H-5), 7.60 (s, 2H, H-2), 7.37 (dd, 2H, $J_{6,5/6,2}$ = 7.5 Hz, H-6), 3.87 (s, 12H, OCH_3), EI MS: *m*/*z* (rel. abund.%), 328 (M^+, 38), 297 (3), 191 (54), 151 (20) 79 (100), 77 (71). Anal. Calcd for $C_{16}H_{16}N_2O_2$, C = 71.62, H = 6.01, N = 10.44. Found: C = 71.60, H = 6.00, N = 10.43.

*3.2.2.4. 3,4,5-Trimethoxybenzaldehyde-N-[-(3,4,5-trimethoxyphenyl) methylidene] hydrazone (**4**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.57 (s, 2H, –N=CH), 7.72 (s, 2H, H-2), 7.60 (s, 2H, H-6), (s, 18H, OCH_3), EI MS: *m*/*z* (rel. abund.%), 388 (M^+, 38), 257 (3), 191 (54), 151 (20) 79 (100), 77 (71). Anal. Calcd for $C_{20}H_{24}N_2O_6$, C = 61.84, H = 6.23, N = 7.21. Found: C = 61.80, H = 6.20, N = 7.21.

*3.2.2.5. 2-Ethoxybenzaldehyde-N-[-(2-ethoxyphenyl)methylidene] hydrazone (**5**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.04 (s, 2H, –N=CH), 8.10 (dd, 2H, $J_{6,4}$ = 3 Hz $J_{6,5}$ = 9 Hz, H-6), 7.47 (m, 2H, H-4),(d, 2H, $J_{3,4}$ = 8.1 Hz, H-3),(t, 2H, $J_{5,(4,6)}$ = 7.5 Hz, H-5), 4.21 (q, 4H, $-CH_2$), 1.47 (t, 6H, $-CH_3$); EI MS: *m*/*z* (rel. abund.%), 298 (M^+, 9),165 (60), 135 (20), 118 (25), 74 (54). Anal. Calcd for $C_{18}H_{20}N_2O_2$, C = 72.95, H = 6.80, N = 9.45. Found: C = 72.92, H = 6.79, N = 9.43.

*3.2.2.6. 4-Ethoxybenzaldehyde-N-[-(4-ethoxyphenyl)methylidene] hydrazone (**6**).* Yield 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.57 (s, 1H, –N=CH), 7.83, (d, 2H, $J_{6,5/2,3}$ = 8.7 Hz, H-6/2), 7.02 (d, 2H, $J_{5,6/3,2}$ = 8.7 Hz, H-3/5), 4.16 (q, J = 7 Hz, 4H, OCH_2), 1.41(t, 6H, CH_3); EI MS: *m*/*z* (rel. abund.%), 296 (M^+, 87), 269 (15), 175 (100), 133 (90), 120 (56), 77 (20). Anal. Calcd for $C_{18}H_{20}N_2O_2$, C = 72.95, H = 6.80, N = 9.45. Found: C = 72.92, H = 6.79, N = 9.43.

*3.2.2.7. 2-Chlorobenzaldehyde-N-[2-chlorophenyl)methylidene] hydrazone (**7**).* Yield: 78%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.04 (s, 2H, –N=CH), 8.24 (d, 2H, $J_{3,4}$ = 7.8 Hz, H-3), 7.56 (m, 6H, H-4/5/6), EI MS: *m*/*z* (rel. abund.%), 277 (M^+, 5), 240 (46), 206 (47), 129 (18), 75 (100). Anal. Calcd for $C_{14}H_{10}Cl_2N_2$, C = 60.67, H = 3.64, N = 10.11. Found: C = 60.66, H = 3.64, N = 10.08.

*3.2.2.8. 3-Chlorobenzaldehyde-N-[-(3-chlorophenyl)methylidene] hydrazone (**8**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.67 (s, 2H, –N=CH), 7.95(br. s, 2H, H-2), 7.93, (dd, 2H, $J_{6,5/6,4}$ = 8.1 Hz, H-6), (m, 4H, H-4/5), EI MS: *m*/*z* (rel. abund.%), 277(M^+, 18), 165 (83), 138 (24), 111(60), 75 (100). Anal. Calcd for $C_{14}H_{10}Cl_2N_2$, C = 60.67, H = 3.64, N = 10.11. Found: C = 60.64, H = 3.63, N = 10.09.

*3.2.2.9. 4-Chlorobenzaldehyde-N-[-(4-chlorophenyl)methylidene] hydrazone (**9**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.67 (s, 2H, –N=CH), 7.56 (d, 4H, $J_{2,3/6,5}$ = 8.7 Hz, H-2/6), 7.94 (d, 4H, $J_{3,2/5,6}$ = 9 Hz, H-3/5), EI MS: *m*/*z* (rel. abund.%), 277 (M^+, 6), 165 (56), 138 (21), 111 (58), 75 (100). Anal. Calcd for $C_{14}H_{10}Cl_2N_2$, C = 60.67, H = 3.64, N = 10.11. Found: C = 60.64, H = 3.63, N = 10.09.

*3.2.2.10. 3-4-Dichlorobenzaldehyde-N-[-(3–4-dichlorophenyl)methylidene]hydrazone (**10**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.68(s, 2H, –N=CH), 8.09 (dd, 2H, $J_{2,6}$ = 1.8 Hz, H-2), 7.90, (dd, 2H, $J_{6,2}$ = 2.1 Hz, $J_{6,5}$ = 8.4 Hz, H-6), 7.70 (d, 2H, $J_{5,6}$ = 8.4 Hz, H-5), EI MS: *m*/*z* (rel. abund.%), 346 (M^+, 9), 246 (6), 199 (60), 145 (53), 123 (100). Anal. Calcd for $C_{14}H_8Cl_4N_2$, C = 48.59, H = 2.33, N = 8.10. Found: C = 48.58, H = 2.31, N = 8.08.

*3.2.2.11. 2-4-Dichlorobenzaldehyde-N-[-(3–4-dichlorophenyl)methylidene]hydrazone (**11**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.97(s, 2H, –N=CH), 8.24 (d, 2H, $J_{6,5}$ = 8.4 Hz, H-6), 7.54, (dd, 2H, $J_{5,3}$ = 2.1 Hz, $J_{5,6}$ = 8.4 Hz, H-5), 7.66 (d, 2H, $J_{3,5}$ = 2.1 Hz, H-3), EI MS: *m*/*z* (rel. abund.%), 346 (M^+, 3), 310 (19), 274 (21), 147 (15), 123 (100). Anal. Calcd for $C_{14}H_8Cl_4N_2$, C = 48.59, H = 2.33, N = 8.10. Found: C = 48.56, H = 2.31, N = 8.06.

*3.2.2.12. 3-Florobenzaldehyde-N-[-(3-florophenyl)methylidene]hydrazone (**12**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.87 (s, 2H, –N=CH), 8.16 (td, 2H, $J_{4,5/4,2/4,6}$ = 7.8 H-4), 7.62, (dd, 2H, $J_{2,4/2,6}$ = 1.8 Hz, H-2), (dd, 2H, $J_{5,6/5,4}$ = 7.5 Hz, H-5),7.27 (dd 2H, $J_{6,5/2,6}$ = 9.0 Hz, H-6) EI MS: *m*/*z* (rel. abund.%), 244 (M^+, 42), 216 (18), 149 (100), 122 (50), 75 (61). Anal. Calcd for $C_{14}H_{10}F_2N_2$, C = 68.85, H = 4.13, N = 11.47. Found: C = 68.82, H = 4.12, N = 11.46.

*3.2.2.13. 2-Fluorobenzaldehyde-N-[-(2-fluorophenyl)methylidene] hydrazone (**13**).* Yield: 88%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.74 (s, 1H, –N=CH), 8.06 (dd, 2H, $J_{3,4/3,5}$ = 8.7 Hz, H-3), 7.40 (m, 4H, H-4/5), 7.03 (t, 2H, $J_{6,(5,7)}$ = 7.50 Hz, H-6),; EI MS: *m*/*z* (rel. abund.%), 267 (M^+, 7), 239 (100), 212 (9), 118 (76), 95 (71). Anal. Calcd for $C_{14}H_{10}F_2N_2$, C = 68.85, H = 4.13, N = 11.47. Found: C = 68.82, H = 4.11, N = 11.45.

*3.2.2.14. 2-Furaldehyde-N-[-2-furylmethylidene]hydrazone (**14**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.47(s, 2H, –N=CH), 7.79 (d, 2H, $J_{2,3}$ = 3.0 Hz, H-2), 7.06 (d, 2H, $J_{4,3}$ = 3.3 Hz, H-4), 7.54 (dd, 2H, $J_{3,2/3,4}$ = 3.6 Hz, H-3); EI MS: *m*/*z* (rel. abund.%), 188 (M^+, 100),131 (37), 94 (40), 52 (50). Anal. Calcd for $C_{10}H_8N_2O_2$, C = 63.82, H = 4.28, N = 14.89. Found: C = 63.79 H = 4.26, N = 14.85.

*3.2.2.15. 3-Thiophenecarbaldehyde-N-[-3-thienylmethylidene]hydrazone (**15**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.67 (s, 2H, –N=CH), 8.10 (s, 2H, H = 2), 7.67 (d, 4H, $J_{4,5}$ = 3.0 Hz, H-4), 7.54 (d, 4H, $J_{5/4}$ = 3.6 Hz, H-5); EI MS: *m*/*z* (rel. abund.%), 219 (M^+, 63),192 (40), 174 (35), 110 (100). Anal. Calcd for $C_{10}H_8N_2S_2$, C = 54.52, H = 3.66, N = 12.72. Found: C = 54.50, H = 3.65, N = 12.69.

*3.2.2.16. 2-Nitrobenzaldehyde-N-[-(2-nitrophenyl)methylidene] hydrazone (**16**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ9.05 (s,1H, –N=CH), 8.30 (dd, 1H, $J_{3,5}$ = 1.5 Hz, $J_{3,4}$ 7.5 Hz, H-3), 7.91 (td, 1H, $J_{4,5/4,3}$ = 7.8 Hz, H-4), 7.83 (m, 2HH-5), 8.17 (dd, 1H, $J_{6,4}$1.2 Hz, $J_{6,5}$ = 7.8 Hz, H-6);; EI MS: *m*/*z* (rel. abund.%), 294 (M^+, 6), 298 (68), 206 (22), 135 (100), 103 (40), 91 (100). Anal. Calcd for $C_{14}H_{10}N_4O_4$, C = 56.38, H = 3.38, N = 18.78. Found: C = 56.36, H = 3.36, N = 18.74.

*3.2.2.17. 3-Nitrobenzaldehyde-N-[-(3-nitrophenyl)methylidene] hydrazone (**17**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.40 (s, 2H, –N=CH), 8.65 (dd. 2H, $J_{2,4/2,6}$ = 1.8 Hz, H-2), 8.32, (m, 2H, H-4), (m, 2H, H-5), (dd, 2H, $J_{6,5/6,2}$ = 8.1 Hz, H-6), EI MS: *m*/*z* (rel. abund.%), 298(M^+, 24), 165(28), 118(58), 89(100). Anal. Calcd for $C_{14}H_{10}N_4O_4$, C = 56.38, H = 3.38, N = 18.78. Found: C = 56.35, H = 3.36, N = 18.75.

*3.2.2.18. 2-Napthaldehyde-N-[-(2-napthyl)methylidene]hydrazone (**18**).* Yield: 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.44 (s, 2H, –N=CH), 8.11 (s, 2H, H-), 8.10 (m, 4H, H-5/8), 7.99 (m, 4H, H-6/7) 7.61 (m, 4H, H-3/4); EI MS: *m*/*z* (rel. abund.%), 308 (M^+, 41), 281 (51), 181(61), 172 (44), 154 (28), 127 (100). Anal. Calcd for $C_{22}H_{16}N_2$, C = 85.69, H = 5.23, N = 9.08. Found: C = 85.67, H = 5.2, N = 9.07.

*3.2.2.19. 4-(Methylsulfanyl)benzaldehyde-N-{-[4-(methylsulfanyl) phenyl] methylidene}hydrazone (**19**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.61 (s, 2H, –N=CH), 7.83 (d, 4H, $J_{2,3/6,5}$ = 8.4 Hz, H-2/6), 7.37 (d, 4H, $J_{3,2/5,6}$ = 8.4 Hz, H-3/5), EI MS: *m*/*z* (rel. abund.%), 300 (M^+, 58), 177 (100), 150 (44), 77 (52). Anal. Calcd for $C_{14}H_{10}N_2S_2$, C = 63.96, H = 5.37, N = 9.32. Found: C = 63.92, H = 5.36, N = 9.29.

*3.2.2.20. 4-(Dimethylamino)benzaldehyde-N-{[(dimethylamino) phenyl] methylidene} hydrazone (**20**).* Yield: 96%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.48 (s, 2H, –N=CH), 7.70 (d, 4H, $J_{2,3/6,5}$ = 9.8 Hz, H-2/6), 6.80 (d, 4H, $J_{3,2/5,6}$ = 8.7 Hz, H-3/5), 3.03 (s, 6H, N(CH_3)$_2$); EI MS: *m*/*z* (rel. abund.%), 294 (M^+, 83), 266 (62), 174 (35), 119 (65), 77 (100). Anal. Calcd for $C_{18}H_{22}N_4$, C = 73.44, H = 7.53, N = 19.03. Found: C = 73.41, H = 7.51, N = 19.02.

*3.2.2.21. Benzaldehyde-N-[phenylmethylidene]hydrazone (**21**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.67 (s, 1H, –N=CH), 7.92, (dd, 2H, $J_{2,3/6,5}$ = 2.1 $J_{2,3/6,5}$ = 9 Hz, H-2/6), 7.52 (m 6H, H-3/4/5),; EI MS: *m*/*z* (rel. abund.%), 208 (M^+, 100), 180 (35), 131 (76), 104 (28). Anal. Calcd for $C_{14}H_{12}N_2$, C = 80.74, H = 5.81, N = 13.45. Found: C = 80.73, H = 5.79, N = 13.44.

*3.2.2.22. 2-Hydroxybenzaldehyde-N-[2-hydroxyphenyl)methylidene] hydrazone (**22**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.92 (s, 1H, –N=CH), 7.97, (dd, 2H, $J_{6,4}$ = 1.5 $J_{6,5}$ = 7.2 Hz, H-6), 7.58 (m, 2H, H-5), 7.12, (d, 2H, $J_{3,4}$ = 8.4 Hz, H-3), 7.05, (t, 2H, $J_{4,(5,6)}$ = 7.5 Hz, H-4; EI MS: *m*/*z* (rel. abund.%), 268 (M^+, 26), 237 (100), 150 (64), 119 (100), 91 (68), 77 (30). Anal. Calcd for $C_{14}H_{12}N_2O_2$ C = 69.99, H = 5.03, N = 11.66. Found: C = 69.98, H = 5.01, N = 11.64.

*3.2.2.23. 2-Methylbenzaldehyde-N-[-(2-methylphenyl)methylidene] hydrazone (**23**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.94 (s, 2H, –N=CH), 8.03, (dd, 2H, $J_{6,4}$ = 1.8 $J_{6,5}$ = 9.0 Hz, H-6), 7.40 (m, 6H,3/4/5), 2.57 (s, 6H, –CH_3)EI MS: *m*/*z* (rel. abund. %), 236 (M^+, 10), 221 (7), 145 (8), 117 (100), 91 (56), 65 (75). Anal. Calcd for $C_{16}H_{16}N_2$, C = 81.32, H = 6.82, N = 11.85. Found: C = 81.30, H = 6.79, N = 11.84.

*3.2.2.24. 4-Methylbenzaldehyde-N-[-(4-methylphenyl)methylidene] hydrazone (**24**).* Yield: 97%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.48 (s, 2H, –N=CH), 7.79 (d, 4H, $J_{2,3/6,5}$ = 8.1 Hz, H-2/6), 6.80 (d, 4H, $J_{3,2/5,6}$ = 7.8 Hz, H-3/5); EI MS: *m*/*z* (rel. abund.%), 236 (M^+, 28), 266 (62), 208 (19), 145 (100), 91(79). Anal. Calcd for $C_{16}H_{16}N_2$, C = 81.32, H = 6.82, N = 11.85. Found: C = 81.30, H = 6.79, N = 11.84.

4. Conclusion

In summary, we have developed an efficient, fast, high yielding, economical synthetic process for the synthesis of *Bis*-Schiff bases. Our methodology could also find uses in the synthesis of libraries for the production of novel *Bis*-Schiff bases with applications in analytical chemistry as well as medicinal chemistry.

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References

[1] A. Masunari, L.C. Tavares, A new class of nifuroxazide analogues synthesis of 5-nitrothiophene derivatives with antimicrobial activity against multidrug-resistant *Staphylococcus aureus*, Bioorg. Med. Chem. 15 (2007) 4229–4236.
[2] M.J. Hearn, M.H. Cynamon, M. Chen, F.R. Coppins, J. Davis, H.J. Kang, A. Noble, B.M. Tu-Sekine, S. Terrot, D. Trombino, M. Thai, E.R. Webster, R. Wilson, Preparation and antitubercular activities *in vitro* and *in vivo* of novel schiff bases of isoniazid, Eur. J. Med. Chem. 4 (2009) 4169–4178.
[3] A.R. Todeschini, A.L. Miranda, C.M. Silva, S.C. Parrini, E.J. Barreiro, Synthesis and evaluation of analgesic, antiinflammatory and antiplatelet properties of new pyridylarylhydrazone derivatives, Eur. J. Med. Chem. 33 (1998) 189–199.
[4] P.C. Lima, L.M. Lima, K.C. Silva, P.H. Leda, A.L.P. Miranda, C.A.M. Fraga, E.J. Barreiro, Synthesis and analgesic activity of novel *N*-acylhydrazones and isosters, derived from natural safrole, Eur. J. Med. Chem. 35 (2000) 187–203.
[5] S. Gemma, G. Kukreja, C. Fattorusso, M. Persico, M. Romano, M. Altarelli, L. Savini, G. Campiani, E. Fattorusso, N. Basilico, Synthesis of N^1-arylidene-N^2-quinolyl- and N^2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant P. *Falciparum strains*, Bioorg. Med. Chem. 16 (2006) 5384–5388.
[6] L. Schirch, A. Slotter, Spectral properties of schiff bases of amino acid esters with pyridoxal and pyridoxal *N*-methochloride in ethanol, Biochemistry 5 (1966) 3172–3186.
[7] F.D. Popp, W. Kirsch, Synthesis of potential anticancer agents. Schiff bases and related compounds, J. Org. Chem. 26 (1961) 3858–3860.
[8] S. Kumar, M.S. Niranjan, K.C. Chaluvaraju, C.M. Jamakhandi, D. Kadadevar, Synthesis and antimicrobial study of some schiff bases of sulfonamides, J. Curr. Pharm. Res. 1 (2010) 39–42.
[9] U.K. Mazumder, M. Gupta, A. Bera, S. Bhattacharya, S. Karki, L. Manikandan, Synthesis, antitumor and antibacterial activity of some Ru(Bpy)2+2/4-substituted thiosemi-carbazide complexes, Indian J. Chem. 42A (2003) 313–317.
[10] M. Tarafder, T. Kasbollah, A.N. Saravanan, K.A. Crouse, A.M. Ali, T. OoK, S-methyldithiocarbazate and its schiff bases: Evaluation of bondings and biological properties, J. Biochem. Mol. Biol. Biophys. 6 (2002) 85–91.
[11] M. Verma, S.N. Pandeya, K.N. Singh, J.P. Stables, Anticonvulsant activity of schiff bases of isatin derivatives, Acta Pharm. 54 (2004) 49–56.
[12] P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Poni, C.A. Cabrasc, P.L. Collac, Synthesis and biological evaluation of benzo[*d*]isothiazole, benzothiazole and thiazole schiff bases, Bioorg. Med. Chem. 11 (2003) 4785–4789.
[13] A. Kasabe, V. Mohite, J. Ghodake, J. Vidhate, Synthesis, Characterization and Primary Antimicrobial, Antifungal Activity Evaluation of Schiff bases of 4-Chloro-(3-Substitutedphenylimino)-methyl-[2*H*]-chromene-2-one, Eur. J. Chem. 7 (2010) 377–382.
[14] M.A. Neelakantan, M. Esakkiammal, S.S. Mariappan, J. Dharmaraja, T. Jeyakumar, Synthesis, characterization and biocidal activities of some schiff base metal complexes, Indian J. Pharm. Sci. 72 (2010) 216–222.
[15] S. Arulmurugan, H.P. Kavitha, B.R. Venkatraman, Biological activities of schiff base and its complexes. A review, Rasāyan J. Chem. 3 (2010) 385–410.
[16] Z.H. Chohan, M. Arif, M. Sarfraz, Metal-based antibacterial and antifungal amino acid derived schiff bases: their synthesis, characterization and *in vitro* biological activity, Appl. Organomet. Chem. 21 (2007) 294–302.
[17] N. Iqbal, J. Iqbal, M. Imran, Synthesis, characterization and antibacterial studies of some metal complexes of a schiff base derived from benzaldehyde and sulphonamide, J. Sci. Res. 31 (2009) 15–19.
[18] R.M. Wang, N.P. He, P.F. Song, Y.F. He, L. Ding, Z. Lei, Preparation of low molecular-weight chitosan derivative zinc complexes and their effect on the growth of liver cancer cells. In vitro, Pure Appl. Chem. 81 (2009) 2397–2405.
[19] R.M. Wanga, N.P. Hea, P.F. Songa, Y.F. Hea, L. Ding, Z.Q. Lei, Preparation of Nano–Chitosan schiff-base copper complexes and their anticancer activity, Polym. Adv. Technol. 20 (2009) 959–964.
[20] G. Kumar, D. Kumar, S. Devi, R. Verma, R. Johari, Synthesis, spectral characterization of biologically active compounds derived from oxalyldihydrazide and 5-*tert*-butyl-2-hydroxy-3-(3-phenylpent-3-yl) benzaldehyde and their Cu(II), Ni(II) and Co(II) complexes, Int. J. Eng. Sci. Technol. 3 (2011) 1630–1635.
[21] Y.N. Xioa, C.X. Zhan, Studies on the interaction of dna and water-soluble polymeric schiff base-Nickel complexes, J. Appl. Polym. Sci. 84 (2002) 887–893.
[22] A.P. Mishra, M. Soni, Synthesis, structural, and biological studies of some schiff bases and their metal complexes, Met.-Based Drugs II (875410) (2008) 1–7.
[23] Z.H. Chohan, H. Pervaiz, M.K. Khan, A. Rauf, G.M. Maharvi, C.T. Supran, Antifungal Co(II), Cu(II), Ni(II) and Zn(II) complexes furunyl-thiophenyl, pyroloyl, salisylyl, and pyridyl derived cephalaxcin, J. Enzym. Inhib. Med. Chem. 19 (2004) 85–90.
[24] K.S. Siddiqi, R.I. Kureshy, N.H. Khan, S. Tabassum, S.A.A. Zaidi, Characterization and toxicity of lanthanide complexes with nitrogen and sulphur containing schiff bases, Inorg. Chim. Acta 151 (1988) 95–100.

[25] M. Du, Y. Wang, X. Zhang, C. Zhang, Highly sensitive spectrofluorimetric determination of trace amounts of scandium with salicylaldehyde salicyloylhydrazone, Analyst 123 (1998) 283–286.
[26] W. Tang, Y. Xiang, A. Tong, Salicylaldehyde azines as fluorophores of aggregation-induced emission enhancement characteristics, J. Org. Chem. 74 (2009) 2163–2166.
[27] Y. Wang, H. Lin, J. Shao, Z. Cai, H.A. Lin, Phenylhydrazone-based indole receptor for sensing acetate, Talanta 74 (2008) 1122–1125.
[28] J.H. Billman, K.M. Tai, Reduction of schiff bases II. Benzhydrylamines and structurally related compounds, J. Org. Chem. 23 (1958) 535–539.
[29] H. Weingart, J.P. Chupp, W.A. White, Versatile new enamine synthesis, J. Org. Chem. 32 (1967) 213–214.
[30] S.M. Landge, V. Atanassova, M. Thimmaih, B. Torok, Microwave-assisted oxidative coupling of amines to imines on solid acid catalysts, Tetrahedron Lett. 48 (2007) 5161–5164.
[31] S. Perveen, S. Mustafa, K.M. Khan, An unplanned synthesis of symmetrical 1,3-disubstituted ureas, J. Chem. Soc. Pak. 32 (2010) 229–234.
[32] K.M. Khan, A. Ahmad, N. Ambreen, A. Amyn, S. Khan, S. Perveen, M.I. Choudhary, Schiff bases of 3-formylchromones as antibacterial, antifungal, and phytotoxic agents, Lett. Drug Des. Discov. 6 (2009) 363–373.
[33] K.M. Khan, U.R. Mughal, N. Ambreen, A. Khan, S. Perveen, M.I. Choudhary, Schiff bases of istain: antiglycation activity, Lett. Drug Des. Discov. 6 (2009) 358–362.
[34] K.M. Khan, M. Ali, T.A. Farooqui, M. Khan, M. Taha, S. Perveen, An improved method for the synthesis of 5-arylidene barbiturates using $BiCl_3$, J. Chem. Soc. Pak. 31 (2009) 823–828.
[35] K.M. Khan, Z. Shah, V.U. Ahmad, N. Ambreen, M. Khan, M. Taha, F. Rahim, S. Noreen, S. Perveen, M.I. Choudhary, W. Voelter, 6-Nitrobenzimidazole derivatives: potential phosphodiesterase inhibitors: synthesis and structure-activity relationship, Bioorg. Med. Chem. 20 (2012) 1521–1526.
[36] B.P. Branchaud, Studies on the preparation and reactions of tritylsulfenimines, J. Org. Chem. 48 (1983) 3531–3538.
[37] A.K. Chakraborti, S. Bhagat, S. Rudrawar, Magnesium perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones, Tetrahedron Lett. 45 (2004) 7641–7644.
[38] A. Bazgir, Microwave-assisted efficient synthesis of diimines in dry media using silica gel supported sodium hydrogen sulfate as reusable solid support, J. Chem. Res. 1 (2006) 1–2.
[39] (a) E. Ruiz, H. Rodríguez, J. Coro, E. Salfrán, M. Suárez, R. Martínez-Alvarez, N. Martín, Ultrasound-assisted one-pot, four component synthesis of 4-aryl 3,4-dihydropyridone derivatives, Ultrason. Sonochem. 18 (2011) 32–36;
(b) G. Cravotto, P. Cintas, Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications, Chem. Soc. Rev. 35 (2006) 180–196.
[40] (a) H. Kumar, A. Parmar, Ultrasound promoted $Zrcl_4$ catalyzed rapid synthesis of substituted 1, 2, 3, 4-tetrahydropyrimidine-2-ones in solvent or dry media, Sonochemistry 15 (2008) 129–132;
(b) R. Cella, H.A. Stefani, Ultrasound in Heterocycles Chemistry, Tetrahedron 65 (2009) 2619–2641.
[41] G. Sabitha, E.V. Reddy, C. Maruthi, J.S. Yadav, Bismuth(III) chloride-catalyzed intramolecular Hetero–Diels–Alder Reactions: a novel synthesis of hexahydrodibenzo[*b*, *h*][1,6]naphthyridines, Tetrahedron Lett. 43 (2002) 1573–1575.
[42] H.B. Sun, B. Li, R.M. Hua, Y.W. Yin, An efficient and selective hydroarylation of styrenes with electron-rich arenes, catalyzed by Bismuth(III) chloride and affording markovnikov adducts, Eur. J. Med. Chem. 46 (2006) 4231–4236.
[43] A. McCluskey, S.K. Leitch, J. Garner, C.E. Caden, T.A. Hill, L.R. Odell, S.G. Stewart, S.G. Stewart, $BiCl_3$-mediated opening of epoxides, a facile route to chlorohydrins or amino alcohols: one reagent, two paths, Tetrahedron Lett. 46 (2005) 8229–8232.
[44] Z.-P. Zhan, J.-L. Yu, W.-Z. Yang, An effective bismuth trichloride-catalyzed synthesis of 1,8-dioxo-octahydroxanthenes, Synth. Commun. 36 (2006) 1373–1382.
[45] C.S. Jia, G.W. Wang, Efficient solvent-free synthesis of quinolines promoted by $BiCl_3$, Lett. Org. Chem. 3 (2006) 289–291.