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Thiamine hydrochloride: An efficient catalyst for one-pot synthesis of quinoxaline derivatives at ambient temperature

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Abstract. Quinoxaline derivatives have been synthesized in high to excellent yields in the presence of thiamine hydrochloride (VB_1) as an inexpensive, non-toxic and metal ion free catalyst at ambient temperature.

Keywords. Quinoxalines; aryl-1,2-diamines; 1,2-diketones; thiamine hydrochloride.

1. Introduction

Quinoxaline and its derivatives have been received much attention because of their wide range of pharmacological and therapeutic properties.[1–8] They have also been found applications in organic semiconductors,[9] dyes,[10] electroluminescent materials,[1] cavitands,[11] building blocks for the synthesis of anion receptors[12] and DNA cleaving agents.[12] Therefore, several methods for the synthesis of quinoxalines have been reported in the literature.[13–32] However, some of these reported methods are associated with one or more disadvantages such as harsh reaction conditions, use of expensive reagents, use of environmentally toxic reagents and use of large amount solid supports, which result in the generation of a large amount of toxic waste. Thus, several previous methods have been excluded from practical applications due to environmental and economic considerations. Hence, there is still a need to develop efficient methods for the synthesis of quinoxaline derivatives.

Thiamine hydrochloride is a non-toxic, inexpensive, stable, eco-friendly and metal ion free catalyst. Thiamine hydrochloride has been used as powerful catalyst for various organic transformations.[33–35] The structure of thiamine hydrochloride contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (figure 1).

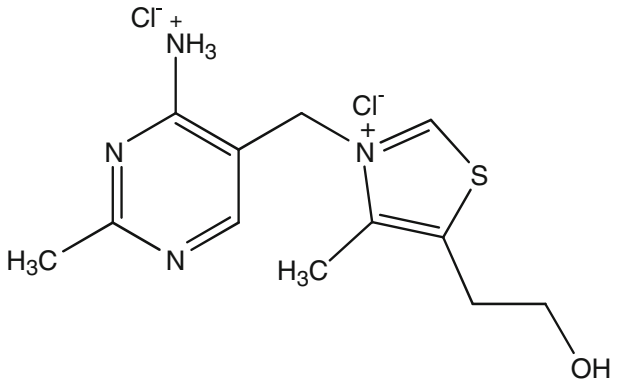


Figure 1. Structure of thiamine hydrochloride.

2. Experimental

2.1 *General remarks*

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were determined on a Perkin-Elimer spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature on Varian Inova spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded on an automated Shimadzu QP 5050 mass spectrometer. Reactions were monitored by TLC on aluminum sheets pre-coated with silica gel $60F_{254}$.

2.2 *General procedure for the synthesis of quinoxaline derivatives*

A mixture of aryl-1,2-diamine **1** (1 mmol), 1,2-diketone **2** (1 mmol) and VB_1 (2 mol%) in ethanol (2 mL)

*For correspondence

was stirred at room temperature for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice cold water. The solid was filtered and purified by column chromatography on silica gel (ethyl acetate/*n*-hexane) to afford the pure product. The desired pure product(s) were characterized by comparison of their physical data with those known compounds.[13–32]

2.3 *Characterization data of compounds*

3a: mp 127–129°C [Lit.[19] mp 126–127°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.40 (m, 6 H, ArH), 7.45–7.56 (m, 4 H, ArH), 7.73–7.81 (m, 2 H, ArH), 8.15–8.24 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 128.21, 128.73, 128.96, 129.79, 129.93, 139.02, 141.22, 153.01; IR (KBr, Cm^{-1}): 697, 757, 820, 1056, 1216, 1340, 1473, 1540, 1569, 1600, 3060; Calcd for $C_{20}H_{14}N_2$ (282): C 85.08, H 5.00, N 9.92%. Found: C 85.20, H 5.02, N 9.85%.

3c: mp 192–194°C [Lit.[19] mp 193–194°C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.43 (m, 6 H, ArH), 7.53–7.58 (m, 4 H, ArH), 8.29 (d, J = 9.18 Hz, 1H, ArH), 8.53 (dd, J = 9.18 Hz and 2.50 Hz, 1H, ArH), 9.07 (d, J = 2.50 Hz, 1 H, ArH); ^{13}C NMR (75 Mhz, $CDCl_3$): 123.20, 125.50, 128.40, 129.60, 129.70, 129.80, 130.70, 137.91, 138.00; IR (KBr, Cm^{-1}): 669, 836, 928, 1055, 1215, 1342, 1435, 1475, 1527, 1574, 1618, 3020; Calcd for $C_{20}H_{13}N_2O_2$ (327): C 73.38, H 4.00, N 12.85%. Found: C 73.18, H 4.12, N 12.75%.

3. Results and discussion

As a part of our ongoing program on the development of novel synthetic methods in organic synthesis under mild conditions,[36] we wish to report a simple and efficient method for the synthesis of quinoxalines in the presence of thiamine hydrochloride (VB_1) as an inexpensive, non-toxic and metal ion free catalyst at ambient temperature (scheme 1).

To determine the optimum quantity of thiamine hydrochloride, the reaction of *o*-phenylenediamine (1 equiv) and benzil (1 equiv) in ethanol was carried out at room temperature using different quantities of catalyst. The use of 2 mol% of catalyst resulted in the highest yield in 12 min (table 1).

In another study, the efficiency of different solvents upon the model reaction was investigated at room temperature and the results are summarized in the table 2. We observed that in aprotic solvents (entries 1–7, table 2) the product yield was found to be low, but in case of protic solvents (entries 8–10, table 2) the

Table 1. Optimization quantity of VB_1.

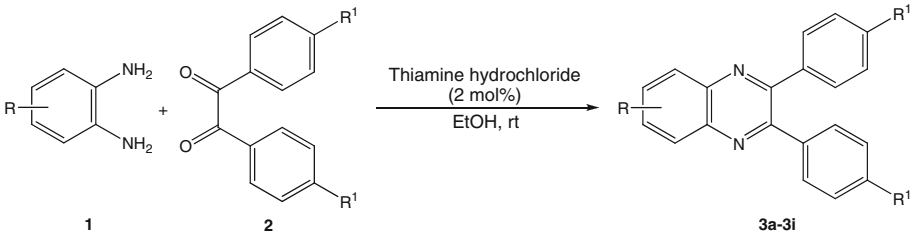
Entry[a]	Catalyst (mol%)	Yield[b](%)
1	0	Trace
2	1	79
3	2	92
4	3	91
5	4	92

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzil (1 mmol), ethanol (2 ml).
[b]Yield of pure, isolated product.

Table 2. Optimization of solvent.

Entry[a]	Solvent	Yield[b](%)
1	1,4-Dioxane	79
2	Chloroform	82
3	DCM	84
4	THF	85
5	DMF	86
6	Acetonitrile	84
7	DMSO	88
8	Ethanol	92
9	Methanol	90
10	Water	89

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzil (1 mmol), VB_1 (2 mol%), solvent (2 ml).
[b]Yield of pure, isolated product.



Scheme 1. Synthesis of quinoxaline derivatives.

reaction rate and product yield was found to be improved comparatively and protic solvent ethanol came out as superior solvent for this reaction.

The efficiency of the VB_1 compared to various catalysts was also examined (table 3). In this study, it was found that VB_1 is an efficient and superior catalyst

Table 3. Comparison of efficiency of various catalysts.

Entry[a]	Catalyst	Solvent	Time (min)	Yield[b](%)
1	$ZnCl_2$ (4 mol%)	Ethanol	20	82
2	I_2 (5 mol%)	Ethanol	10	91
3	Zn[(L)proline] (10 mol%)	Acetic acid	5	88
4	VB_1 (2 mol%)	Ethanol	12	92

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzil (1 mmol), solvent (2 ml).
[b]Yield of pure, isolated product.

Table 4. Thiamine hydrochloride catalysed synthesis of quinoxalines.

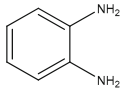
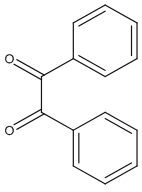
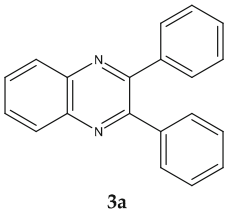
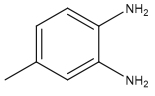
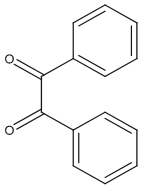
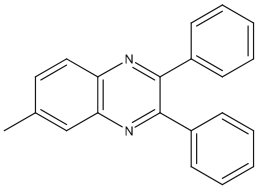
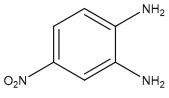
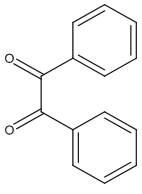
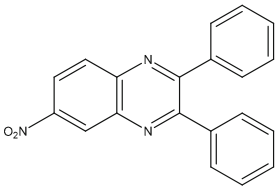
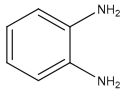
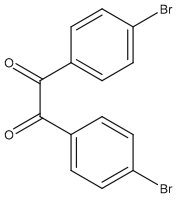
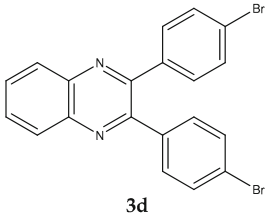
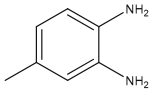
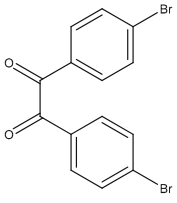
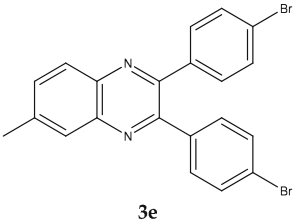
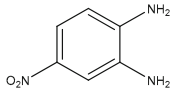
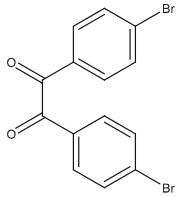
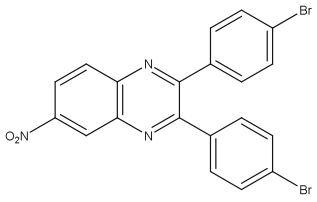
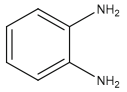
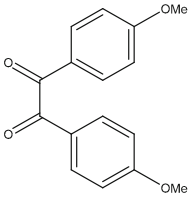
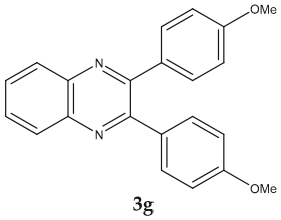
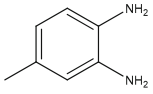
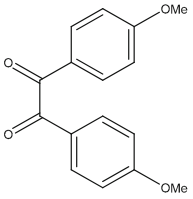
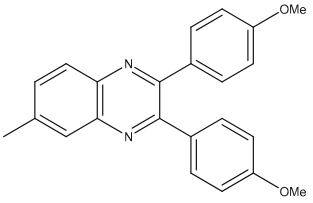
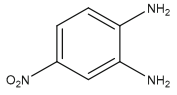
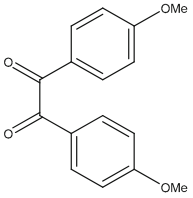
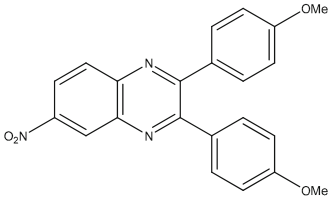
Entry	1,2-diamine 1	1,2-diketone 2	Product[a] 3	Time (Min)	Yield (%)[b]
1			 **3a**	12	92
2			 **3b**	14	92
3			 **3c**	15	87
4			 **3d**	13	94
5			 **3e**	14	93

Table 4. (*continued*)

Entry	1,2-diamine 1	1,2-diketone 2	Product[a] 3	Time (Min)	Yield (%)[b]
6			 **3f**	15	90
7			 **3g**	12	93
8			 **3h**	15	91
9			 **3i**	14	88

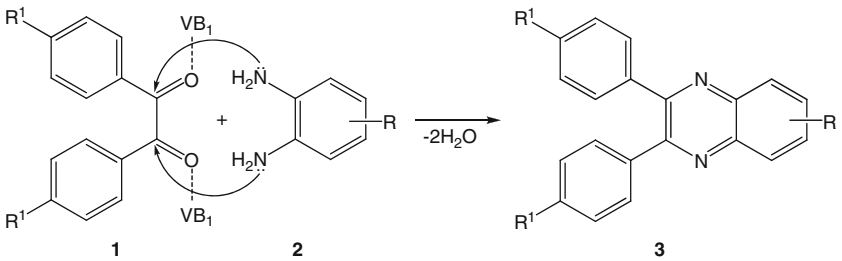
[a]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopic data and their m.p. compared with literature values.[13–32]

[b]Yield of pure, isolated product.

compared to other catalysts with respect to time and yield of product.

To establish the scope of this method various aryl-1,2-diamines were reacted with some 1,2-diketones using optimized conditions (table 4). We observed that electronic-donating groups associated with aryl-1,2-diamines had no significant effect on the reaction results but electron-withdrawing groups slightly decreased the yields and increased the reaction times.

We have not established an exact mechanism for the formation of this kind of compounds **3**; however, a plausible mechanism is shown in scheme 2. The role of the VB_1 may be postulated in terms of the -NH proton of the VB_1, leading to its interaction with the



Scheme 2. Plausible mechanism for the synthesis of quinoxalines.

carbonyl oxygen atom of 1,2-diketone, thereby increasing the polarization and promoting the cyclocondensation reaction.

4. Conclusions

In conclusion, a reliable, rapid and eco-friendly method for synthesis of quinoxalines has been developed, which involves the use of inexpensive, stable, non-toxic and metal-ion free catalyst. Simple work-up, high yields and mild reaction conditions have made this approach superior over many other previously reported methods.

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