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ORIGINAL PAPER

Vitamin B_1 as a metal-ion-free natural catalyst for sustainable quinoxaline ring condensation under sonochemical conditions

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Abstract The role of vitamin B_1 as a catalyst is investigated for the quinoxaline ring condensation under various mild reaction conditions. The results revealed that the combination of vitamin B_1 and ultrasonic irradiation promotes the reaction more efficiently. The salient features of this environmentally benign method are fast conversions, excellent yields for a wide range of substrates, and the use of a low-cost, readily available, nontoxic, and metal-ion-free natural catalyst. The wide range of turnover frequency values (6–400 h^{-1}) shows that the reaction rate is highly dependent on the nature of the functional groups on the aromatic ring of substrates. Moreover, a plausible mechanism for the catalytic action of vitamin B_1 has been introduced.

Keywords Vitamin B_1 · Metal-ion-free natural catalyst · Quinoxalines · Ultrasonic irradiation

Introduction

Vitamin B_1 (VB_1) is an eco-friendly, naturally occurring, widely available, and low-cost substance possessing low toxicity [LD_{50} (VB_1, oral rat) = 3,710 mg kg^{-1}]. The structure of VB_1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). Although the use of thiazoles as a powerful catalyst for various organic transformations has been reported [1–12], few reports in the literature have described the use of VB_1 as a catalyst [13–17]. The ease and safety of handling of VB_1, its water-soluble nature, and ability to act as a biocatalyst make it a potential green catalyst.

The one-step (or direct) double condensation of 1,2-dicarbonyls with benzene-1,2-diamines to afford quinoxalines is an interesting target in modern organic chemistry [18]. These compounds play a key role and have great synthetic potential for application in academia and in many aspects of pharmaceutical and medicinal chemistry [19–28]. The traditional processes for the synthesis of quinoxaline rings generally require high reaction temperature, strong acidic media, and mostly long reaction time in the presence of ethanol or acetic acid and give low to good yields [29].

Recently, a few catalytic reactions have been reported for the preparation of quinoxalines [30–39]. Although these methods have some synthetic advantages individually, they are still plagued by some limitations such as long reaction time [30], the use of toxic [31] or corrosive solvent [32, 33], not readily available materials [31, 33–35], and the use of strong oxidants [36], strong acids [32], and toxic catalysts [37, 38]. Besides, some procedures have restricted activity and are not applicable to the entire family of quinoxaline derivatives, the yields of some products are not satisfactory, and the reactions often require cumbersome product isolation. Therefore, the development of a practical, efficient, and greener alternative using a sustainable protocol is still of interest for the preparation of these compounds.

The use of ultrasound in organic transformation is now well known to enhance reaction rates and yield/selectivity of reactions, and in several cases facilitates organic transformations under ambient conditions which otherwise require drastic conditions of temperature and pressure. The

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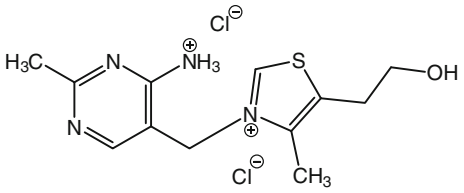


Fig. 1 Structure of vitamin B_1 (VB_1)

driving energy is provided by cavitation, the formation and collapse of bubbles, which liberates considerable energy in short times. It follows then that the molecules that can be activated for sonochemical transformation are those that can penetrate the atmosphere of the bubble, which in turn constitutes a limitation of the method [40–42]. Moreover, sonochemistry shares with sustainable chemistry such aims as the use of less hazardous chemicals and solvents, a reduced energy consumption, and an increased product selectivity [43, 44].

In continuation of our work to develop new catalysts for acid-catalyzed benzo[*N*,*N*]-heterocyclic condensation [45–50], herein we report a mild, efficient, and environmentally benign method for the quinoxaline ring condensation in the presence of VB_1 as a catalyst in methanol under sonochemical conditions.

Recently, the use of VB_1 as a catalyst for the preparation of amidoalkylnaphthols [16] and 3,4-dihydropyrimidin-2(1*H*)-ones [17] under ultrasound irradiation was reported.

Results and discussion

In an initial study to evaluate the catalytic activity of VB_1, we deliberately chose a strong electron-withdrawing group such as nitro on the aromatic ring of benzene-1,2-diamine for the model reaction. The reason for this judicious choice was that the strong electron-withdrawing property of the nitro group in 4-nitrobenzene-1,2-diamine noticeably decreases the nucleophilicity of the amino group, hence longer reaction time is required [45–48, 51, 52].

Role of VB_1 under various reaction conditions

The role of VB_1 as a catalyst for the reaction of 4-nitrobenzene-1,2-diamine (1.1 mmol) and benzil (1 mmol) in MeOH for a fixed time (1 h) was investigated (Scheme 1). The results are shown in Table 1. The uncatalyzed reaction under ambient (i.e., room temperature, RT), thermal, and sonochemical conditions afforded the product **1d** in 11, 50, and 75% yield, respectively (Table 1, entry 1). When the same reaction was catalyzed by VB_1 (5 mol%) the reaction yield sharply increased under various conditions (Table 1, entry 2); e.g., in the presence of VB_1 as a catalyst, product **1d** was obtained in 60% yield (instead of 11%) at room temperature. Accordingly, the combination of VB_1 and ultrasonic irradiation exhibited the highest conversion rate and afforded the product **1d** in 96%.

Catalyst loading and choice of solvent

In the study of catalyst loading, the effect of the relative amounts of VB_1 on the outcome of the model reaction was also studied. Increased loading of the catalyst from 1 to 10 mol% for a fixed reaction time (1 h) showed that 5 mol% of VB_1 in MeOH was the optimum catalyst ratio for this conversion leading to quantitative yield of product **1d** (Table 2, entry 3). Lower catalyst loadings gave lower yields, although higher loadings did not cause an obvious increase in the yield of product.

The synthesis of **1d** was then performed in common solvents in the presence of 5 mol% VB_1 under sonication. The reaction did not progress in water and dichloromethane (Table 2, entries 6, 7), whereas the reaction proceeded well in methanol and ethanol (Table 2, entries 3, 5). As the products **1**, unlike VB_1, remain insoluble in aqueous medium, they could be easily separated by removal of solvent, addition of water, and further filtration. Therefore, MeOH [53] stands out as the solvent of choice owing to its easier removal during workup.

Evaluation of reaction scope

These excellent preliminary results led us to expand the generality of this catalyst to various benzene-1,2-diamines and 1,2-dicarbonyls (Scheme 2). Most of the reactions took 3–30 min to complete under sonochemical conditions, although the yields were highly dependent on the substrate used (Table 3). All of the products were characterized by ^{1}H NMR, ^{13}C NMR, and MS spectral analysis. The results show that the nature of the functional group on the aromatic ring of the substrate exerted a strong influence on the time and the reaction yield. To establish the scope and limitations of the catalyst for quinoxaline formation, the condensation between 4-nitrobenzene-1,2-diamine and

Scheme 1

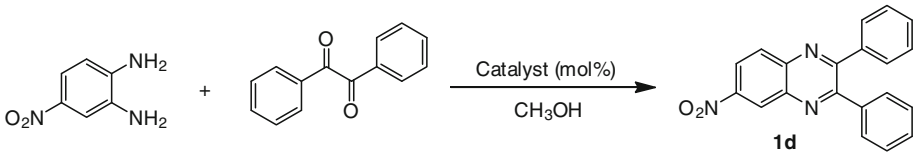
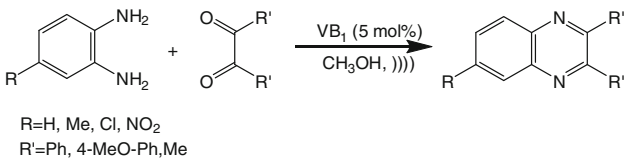


Table 1 Catalytic effect of VB_1 on the model reaction

Entry	VB_1 (mol%)	Time (h)	Conversion without sonication (%)		Conversion with sonication (%)
			RT	40 °C	
1	–	1	11	50	75
2	5	1	60	82	96

Table 2 Optimization of catalyst amount and solvent effect on the model reaction under sonochemical conditions

Entry	VB_1 (mol%)	Conditions (h)	Solvent	Conversion (%)
1	1	))))), 1	CH_3OH	91
2	3	))))), 1	CH_3OH	94
3	5	))))), 1	CH_3OH	96
4	10	))))), 1	CH_3OH	96
5	5	))))), 1	C_2H_5OH	93
6	5	))))), 1	CH_2Cl_2	20
7	5	))))), 1	H_2O	7



Scheme 2

4,4′-dimethoxybenzil was considered. The presence of the methoxy group in 4,4′-dimethoxybenzil reduces the electrophilicity of the carbonyl carbon through resonance and the strong electron-withdrawing property of the nitro group in 4-nitrobenzene-1,2-diamine decreases the nucleophilicity of the amine group. Accordingly, the combination of these substrates provided the corresponding product **1h** in 87% yield within 3 h (Table 3, entry 8).

The turnover frequency (TOF) for this catalytic process, which is defined as mole of converted substrate per mole of catalyst per hour, is listed in Table 3. In most cases moderate to high values of TOF in the range of 40–400 h^{-1} were achieved. Nevertheless, a substantial decrease in the TOF value (6 h^{-1}) is observed for substrates of very low activity (Table 3, entry 8).

There are recent reports of carrying out this reaction in the presence of other catalysts under ambient conditions (Table 4). The data presented in this table show the promising features of this method in terms of reaction rate, product yield, and eco-friendliness.

Taking into account our recent studies on the effect of ammonium salt systems [47], we propose a plausible mechanism for the VB_1-catalyzed double condensation of benzil with benzene-1,2-diamine in Scheme 3. Ammonium sites of the catalyst interact with carbonyl groups of the dicarbonyl compound to form the activated carbonyls of complex **A**. Nucleophilic attack of the diamine on the activated carbonyls in complex **A** produces the intermediate **B**. Eventually, detachment of VB_1 and subsequent loss of water leads to the formation of the quinoxaline ring.

In summary, the use of metal-ion-free natural VB_1 in a catalytic quantity under sonochemical conditions is a general practical alternative to existing procedures for the synthesis of quinoxaline derivatives. The procedure offers several advantages including environmental friendliness, increased variation of substituents in the product with high

Table 3 Evaluation of reaction scope

Entry	R	R′	Product	Time	Conversion (%)	Yield (%)[a]	TOF (h^{-1})[b]	References
1	H	Ph	**1a**	5 min	100	100	240	[49]
2	Me	Ph	**1b**	3 min	100	100	400	[49]
3	Cl	Ph	**1c**	10 min	100	95	120	[54]
4	NO_2	Ph	**1d**	1 h	96	93	19	[49]
5	H	4-MeO-Ph	**1e**	25 min	100	98	48	[45]
6	Me	4-MeO-Ph	**1f**	25 min	100	94	48	[46]
7	Cl	4-MeO-Ph	**1g**	1 h	100	91	20	[36]
8	NO_2	4-MeO-Ph	**1h**	3 h	94	87	6	[46]
9	H	Me	**1i**	5 min	100	95	240	[47]
10	Me	Me	**1j**	5 min	100	94	240	[46, 47]
11	Cl	Me	**1k**	20 min	100	92	60	[47]
12	NO_2	Me	**1l**	30 min	100	94	40	[46, 47]

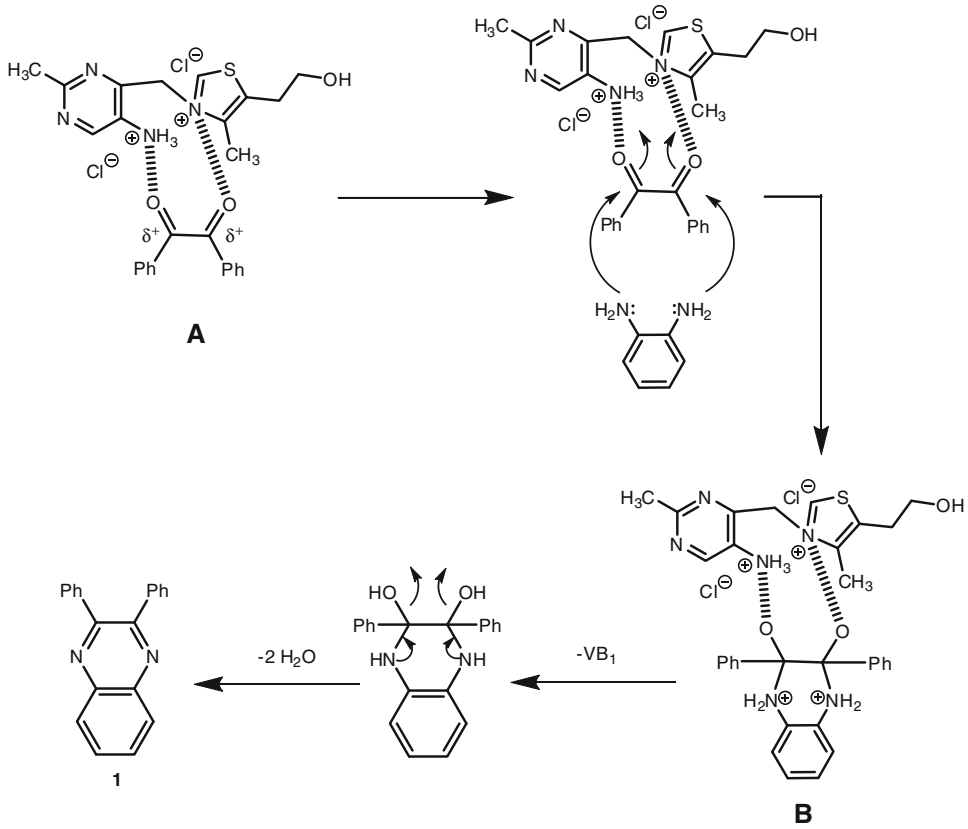
[a] Yields refer to those of pure isolated products characterized by ^1H NMR, ^{13}C NMR, and MS analyses which are consistent with literature values

[b] *TOF* Turnover frequency = mole of converted substrate/(mole of VB_1 × reaction time in hours)

Table 4 Literature results for the synthesis of **1d** at ambient temperature

Entry	Catalyst	Solvent	Reaction time (h)	Isolated yield (%)	Ref.
1	Polyaniline-sulfate (5% w/w)	$ClCH_2CH_2Cl$	0.7	90	[31]
2	Sulfamic acid (80 mol%)	CH_3OH	5	95	[48]
3	Montmorillonite K-10 (10% w/w)	H_2O	6	70	[30]
4	Ammonium chloride (200 mol%)	CH_3OH	4	66	[47]
5	Gallium triflate (1 mol%)	C_2H_5OH	6	90	[39]
6	ZrO_2 (17%)/Ga_2O_3 (4%)/MCM-41	CH_3CN	2	91	[35]
7	$SbCl_3/SiO_2$ (2.5 mol%)	CH_3OH	1	92	[46]
8	Zirconium tetrachloride (5 mol%)	CH_3OH	4	98	[45]
9	))))), VB_1 (5 mol%)	CH_3OH	1	93	This work

Scheme 3



to excellent yields, operational simplicity and, above all, easy purification of products simply by removal of solvent, addition of water, and filtration.

Experimental

The ultrasonic processor used in the experiments was a UP200H from Hielscher-Ultrasound Technology (Germany) equipped with a 2-mm horn tip (Sonotrode S2), with an operating frequency of 24 kHz, and a sonic power density of 480 W/cm^2. The sonic horn was dipped about 1 cm into the solution.

All the employed substrates, catalysts, and solvents were commercially available and used without any further purification. Melting points are determined on Büchi 530. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500-MHz spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were obtained on a Fisons instrument.

General procedure for preparation of quinoxalines under ultrasound irradiation

All reactions were carried out in an open vessel which was kept at 25 °C using a temperature-controlled water bath. The temperature inside the reactor was monitored using a Precision Temperature Logger EBI-2T Type 311 (possessing an external probe) from ebro® Electronic GmbH & Co KG. The recorded temperature within 1 h was 36–37 °C.

A mixture of benzene-1,2-diamine (1.1 mmol), 1,2-diketone (1 mmol), and crystalline VB_1 (5 mol%) was taken in 5 cm^3 methanol and sonicated for the appropriate reaction time (Table 3). After completion of the reaction [monitored by TLC using ethyl acetate/hexane (3:7 v/v) or GC], the organic medium was removed with a rotary evaporator under reduced pressure. Water (10 cm^3) was added to the resulting solid mixture and filtered to afford the product **1**. The crude products were purified by flash chromatography to afford pure products for analytical measurements.

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