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A convenient one-pot synthesis of formamide derivatives using thiamine hydrochloride as a novel catalyst

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ABSTRACT

Formamide derivatives have been synthesized in excellent yields from amine and formic acid in the presence of a catalytic amount of thiamine hydrochloride (VB_1) at 80 °C. The advantages of this method are the use of a cheap, stable, non-toxic, and readily available catalyst, easy work-up, improved yields, and solvent-free conditions.

Formylation of amines is one of the most important protocols in organic synthesis and medicinal chemistry. Formamides are useful intermediates in various organic syntheses as their skeletons are present in different medicinally important compounds.[1] Moreover, the formyl group is an important amino-protecting group in peptide synthesis.[2] In recent years, formamides are also used as Lewis bases to promote several organic transformations.[3]

A number of formylation methods have been reported in recent years. Some of the useful formylation reagents are chloral,[4] formic acid-DCC,[5] formic acid-EDCI,[6] formic acid-$ZnCl_2$,[7] formic acid-PEG 400,[8] formic acid esters,[9] CDMT,[10] and other formylation reagents.[11] However, many of these procedures so far suffer from disadvantages, such as expensive reagents, harsh reaction conditions, prolonged reaction times, high reaction temperature, and low isolation yields. Therefore, there is a need to develop a better catalyst for the synthesis of formamide derivatives in terms of operational simplicity and economic viability.

It is well known that thiamine hydrochloride (VB_1) is cheap, non-toxic, stable, and can be recovered. VB_1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). VB_1 analogs have been used as powerful catalysts for many carbon–carbon and carbon–heteroatom bond formation reactions in good yields.[12] As a part of the ongoing interest in VB_1-catalyzed reaction for various organic transformations,[13] we had the opportunity to further explore its catalytic activity toward the synthesis of formamides. In this Letter, we wish to report a simple but effective procedure for the synthesis of formamide derivatives from amines and formic acid by employing VB_1 as a novel catalyst (Scheme 1).

Initially, we studied the catalytic efficiency of VB_1 for a model reaction using aniline **1a** and formic acid in different reaction conditions (Table 1). It was reported that no reaction was observed

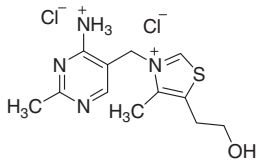
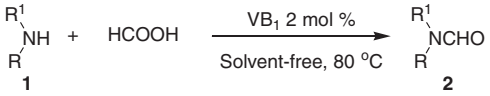


Figure 1. The structure of VB_1.



Scheme 1. Synthesis of formamides **2**.

when a mixture of aniline **1a** and formic acid was heated at 100 °C for 4 h (Table 1, entry 1).[7] However, we obtained the corresponding product **2a** in 84% yield by simply mixing aniline **1a** and formic acid in the presence of 1 mol % of VB_1 at 80 °C for 15 min, thus, highlighting the role of VB_1 as a promoter. Further studies revealed that the reaction was sluggish giving poor yields (<20%) in various solvents, such as MeOH, EtOH, THF, DCM, and MeCN (Table 1, entries 6–10). Moreover, we also found that 2 mol % of VB_1 was sufficient and an excessive amount of catalyst did not increase the yields (Table 1, entries 2–5).

In terms of yields and reaction time, we achieved the best conditions to synthesize formamide **2a** by using 2 mol % VB_1 under solvent-free conditions. Having established the optimized reaction conditions, we then successfully synthesized a variety of formamide derivatives **2** (Scheme 1), and the results are summarized in Table 2.[14]

In all of the studied examples, the aromatic amines, primary amines, and secondary amines could react smoothly to give the

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Table 1
Optimization of the reaction conditions[a]

Entry	Solvent	Catalyst (mol %)	Temp. (°C)	Time (min)	Yield[b] of **2a** (%)
1	None	0	100	240	NR[c,7]
2	None	1	80	15	84
3	None	2	80	10	96
4	None	3	80	10	95
5	None	5	80	10	95
6	MeOH	2	Reflux	240	<20
7	EtOH	2	Reflux	240	<20
8	THF	2	Reflux	240	<15
9	DCM	2	Reflux	240	<10
10	MeCN	2	Reflux	240	<20

[a] Conditions: aniline **1a** (5 mmol), formic acid (1 mL), solvent-free or solvent (3 mL).
[b] Isolated yields.
[c] No reaction was observed.

Table 2
Synthesis of formamides **2** catalyzed by VB_1[a]

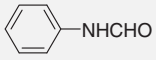
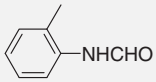
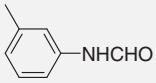
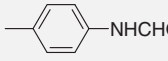
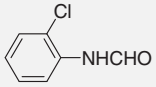
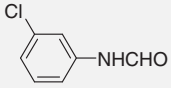
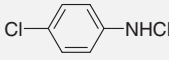
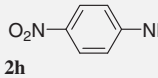
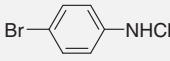
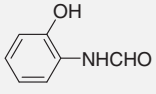
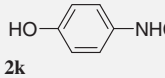
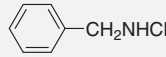
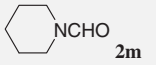
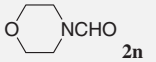
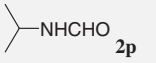
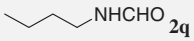
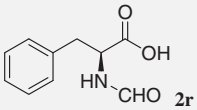
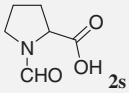
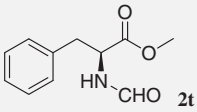
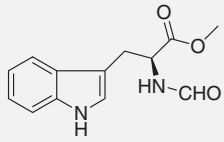
Entry	Product **2**	Time (min)	Yield[b] (%)
1	 **2a**	10	96
2	 **2b**	20	92
3	 **2c**	10	95
4	 **2d**	10	95
5	 **2e**	20	90
6	 **2f**	15	95
7	 **2g**	15	94
8	 **2h**	40	94
9	 **2i**	30	93
10	 **2j**	30	88
11	 **2k**	20	90
12	 **2l**	20	93
13	 **2m**	30	88
14	 **2n**	30	87
15	 **2o**	30	90
16	 **2p**	15	92

Table 2 (*continued*)

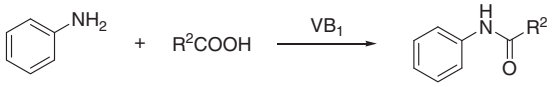
Entry	Product **2**	Time (min)	Yield[b] (%)
	 **2q**		
18	 **2r**	120	0
19	 **2s**	120	0
20	 **2t**	40	85
21	 **2u**	40	85

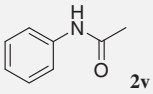
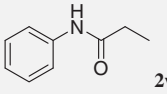
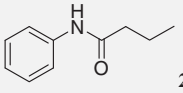
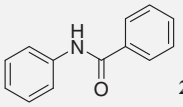
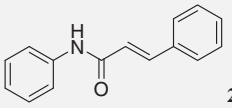
[a] Reaction conditions: amine **1** (5 mmol), formic acid (1 mL), VB_1 (0.1 mmol, 2 mol %), solvent-free, 80 °C.
[b] Isolated yields.

corresponding formamide derivatives **2** in good to excellent yields (85–96%). Aromatic amines carrying either electron-donating or electron-withdrawing groups could react efficiently giving good yields (Table 2, entries 1–11).

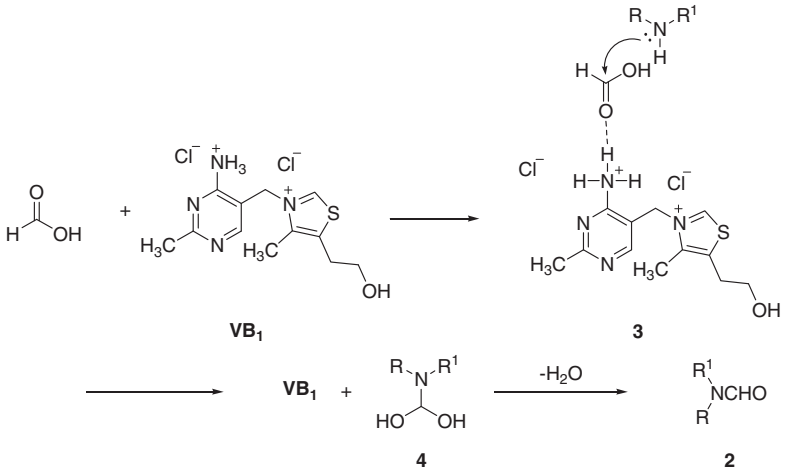
Then, we examined the reactivity of aliphatic amines in the presence of VB_1 (Table 2, entries 12–17). It is interesting to note that in the case of the aliphatic amines, we have achieved good

Table 3
Synthesis of amides **2** catalyzed by VB_1[a]



Entry	Product **2**	Yield[b] (%)
1	 **2v**	90
2	 **2w**	84
3	 **2x**	80
4	 **2y**	0
5	 **2z**	0

[a] Conditions: aniline **1a** (5 mmol), acid (1 mL or 1 g for **2y** and **2z**), VB_1 (0.1 mmol, 2 mol %), solvent-free, 100 °C, 4 h.
[b] Isolated yields.



Scheme 2. A possible mechanism for the formation of compound **2**.

to high yields (88–93%) by employing catalytic amount of VB_1 (2 mol %), which normally show poor yields.[7]

As shown in Table 2, α-amino acids (L-phenylananine and L-proline) were also examined in the presence of 2 mol % of VB_1, unfortunately, no reaction was observed as indicated by TLC. α-Amino acids could not be formylated under the conditions because the α-amino acids were easy to form intramolecular salts which reduced the nucleophilicity of the amino group. Then, we used the carboxyl group-protected α-amino acids (L-phenylalanine methyl ester and L-tryptophan methyl ester) as the starting materials, finding that the reaction could proceed smoothly to give the desired products in good yields.[15]

The reaction that completed within 40 min with excellent yields was an important finding regarding this reaction. The reported methods pointed out that the reaction time was long (4–12 h) when using aromatic amines bearing strong electron-withdrawing group (–NO_2) or secondary amines as the starting materials.[7] However, the reaction could be completed within 40 min using 2 mol % as the catalyst, much shorter than the reported methods.

Furthermore, other carboxylic acids were selected to undergo the amidation (Table 3).[16] The results summarized in Table 3 clearly indicated that the reaction of acetic acid, propionic acid, and butyric acid with aniline in the presence of 2 mol % in 90%, 84%, and 80% yields, respectively, at 100 °C for 4 h.[7] However, no target products were obtained when using benzoic acid and cinnamic acid as starting materials.

We have not established an exact mechanism for the formation of this kind of compounds **2**; however, a reasonable pathway is shown in Scheme 2. Formic acid is activated by VB_1 to form **3**, which reacts to produce the formamide derivatives **2**.

In conclusion, VB_1 has been employed here as an efficient catalyst for the synthesis of formamide derivatives. A simple work-up procedure, mild reaction conditions, and excellent yields make our methodology a valid contribution to the existing methods in the fields of formamide.

Acknowledgments

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14. General procedure for the preparation of formamides **2a**–**2q** and **2t** using VB_1 as a catalyst: A mixture of amine **1** (5 mmol), formic acid (1 mL), and VB_1 (0.1 mmol, 2 mol %) was heated at 80 °C under stirring for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, 20 mL of EtOAc was added and washed with aq HCl (concn 5%), aq Na_2CO_3 (concn 5%), and brine. Then, the organic layer was dried over $MgSO_4$ and concentrated to afford the compounds **2a**–**2q** without further purification.
15. General procedure for the preparation of formamides **2u** using VB_1 as a catalyst: A mixture of L-tryptophan methyl ester (5 mmol), formic acid (1 mL), and VB_1 (0.1 mmol, 2 mol %) was heated at 80 °C under stirring for 40 min. After completion of the reaction as indicated by TLC, 20 mL of EtOAc was added and washed with aq Na_2CO_3 (concn 5%), brine, and concentrated in vacuum to give a course product, which was chromatographed on silica gel and eluted with DCM–MeOH (100:1) to give the pure product **2u**.
Compound **2u**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (br s, 1H), 8.16 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.99 (s, 1H), 6.16 (br s, 1H), 5.03 (dd, J_1 = 5.5 Hz, J_2 = 13.0 Hz, 1H), 3.72 (s, 3H), 3.33–3.34 (m, 2H).
16. General procedure for the preparation of amides **2v**–**2x** using VB_1 as a catalyst: A mixture of aniline **1a** (5 mmol), acid (1 mL), and VB_1 (0.1 mmol, 2 mol %) was heated at 100 °C under stirring for 4 h. After completion of the reaction as indicated by TLC, 20 mL of EtOAc was added and washed with aq HCl (concn 5%), aq Na_2CO_3 (concn 5%), and brine. Then, the organic layer was dried over $MgSO_4$ and concentrated to afford the compounds **2v**–**2x** without further purification.