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An eco-compatible multicomponent strategy for the synthesis of new 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles in aqueous micellar medium promoted by thiamine-hydrochloride

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ABSTRACT

A thiamine hydrochloride (VB_1) accelerated, one-pot synthesis of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles was achieved via four-component reaction of 3-cyanoacetyl indole, aromatic aldehydes, ammonium acetate, and malononitrile in aqueous micellar conditions by a Knoevenagel condensation reaction followed by Michael-addition, which upon cyclization and dehydration yielded the corresponding product in excellent proportion.

Nitrogen containing heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds.[1] One of the most important heterocyclic core moieties is the pyridine ring system which exhibits diverse biological and physiological activities.[2]

Among pyridines, 2-amino-3-cyanopyridine derivatives have raised considerable attention owing to their activity to inhibit PrP^{Sc} accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a),[3a] MAPK-activated PK-2,[3b] and IKK-2 for treating HBV infection,[3c] and modulate androgen receptor function.[3d] In addition, they serve as potassium channel openers for the treatment of urinary incontinence[4] and also act as anti-prion,[3a,5] anti-hepatitis-B virus,[6] anti-bacterial,[7] and anti-cancer[3b] agents. Recently, some of these compounds have been recognized as potential targets for the development of new drugs in the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer[8] and Creutzfeldt–Jakob disease.[3a,5a,9,10]

Another example of the 'privileged scaffolds' is indole framework which is most ubiquitous in nature and also an important structural component in many pharmaceutical agents.[11] Among indoles, 3-substituted indole scaffolds are found in a number of biologically active compounds containing anticancer, antitumour,[12] hypoglycemic, anti-inflammatory, analgesic, and antipyretic activities.[13–20] The wide range of biological activities endowed with pyridines and 3-substituted indole derivatives encouraged us to synthesize novel compounds having additive effect of bioactivities of both privileged scaffolds.

The use of various organic catalysts has gained wide interest in organic synthesis due to their several advantages such as operational simplicity, environmentally benign procedure, recyclability, low cost, and ease of isolation after completion of the reaction.[21]

In this regard, thiamine hydrochloride (VB_1; Fig. 1) analogs, as powerful catalysts have been applied in various organic transformations.[22,23] Currently, several VB_1 catalyzed reactions for the synthesis of heterocyclic compounds such as pyrimidnones,[24] dihydropyridines,[25] benzo[4,5]imidazo[1,2-*a*]pyrimidine/[1,2,4]triazolo[1,5-*a*]pyrimidine,[26a] and quinoxaline derivatives[26b] have been reported.

With the development of modern synthetic approaches, it has been widely acknowledged that there is a growing need for the development of environmentally benign processes in the chemical

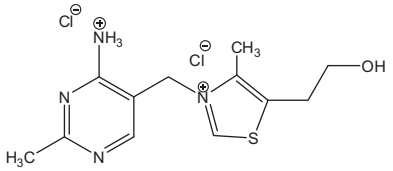

Figure 1. Structure of thiamine-hydrochloride (VB_1).

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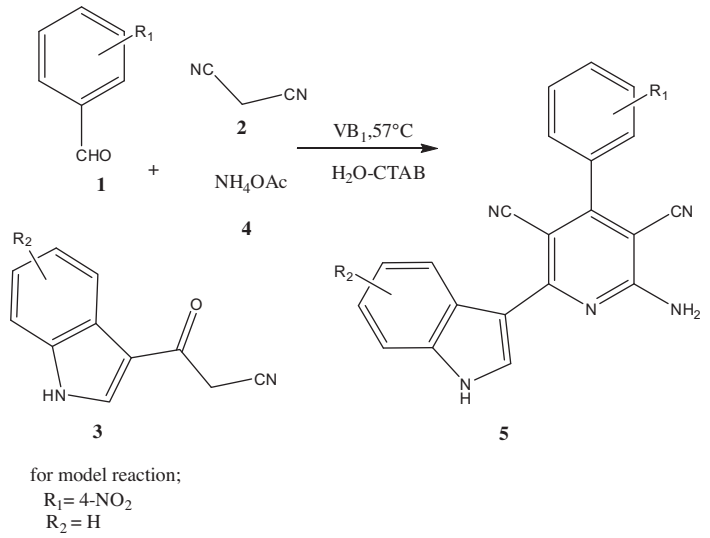
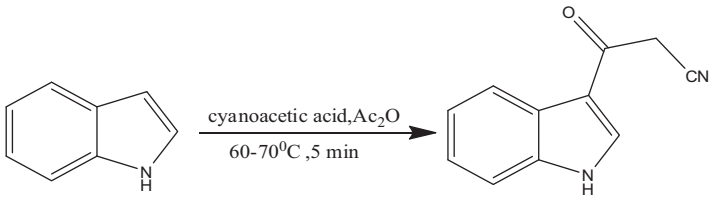


Scheme 1. One pot four-component synthesis of cyanoindolyl pyridines.



Scheme 2.

industry.[27,28] In contrast to this, we noticed that the synthesis of 2-amino, 3-cyano pyridine derivatives is performed mostly in presence of organic solvents such as pyridine and benzene.[29,30] The reaction sometimes involves high temperature, microwave assistance[31] and rare earth metals as catalysts.[32] Although a number of modified methods under improved conditions have been reported, many of them suffer from one or more drawbacks, such as unsatisfactory yields, high temperatures, long reaction times, and the use of toxic organic solvents and catalysts.

Thus, we found it necessary to develop an efficient and convenient method to construct such type of extremely bio-active heterocyclic compounds in aqueous media. Water is the desirable medium for reasons of cost, safety, and environmental impact. Additionally, it can also influence the reaction rate and selectivity due to extensive H-bonding and large dielectric constant.

A powerful approach is the use of aqueous micellar medium to perform various multi-component reactions (MCRs). This approach is of particular importance since it addresses various operational difficulties that can be observed in plain aqueous medium.[33a] Micelles are dynamic clusters of surfactant molecules having both hydrophilic and hydrophobic moieties. They can concentrate the reactants within a small volume, and stabilize substrate, intermediate, or products.[33b] Hence, they offer multiple advantages such as enhanced solubility, reaction rate, regio- and stereo-selectivity, and yield of the products.

Here, VB_1 catalyzed synthesis of novel indolyl pyridine derivatives has been reported in aqueous micellar medium (Scheme 1). The reaction is one-pot, multicomponent and to the best of our knowledge, no reports are available for the synthesis of series of these bioactive compounds.

Compounds such as 3-cyanoacetyl indoles (**3**; which have been used here) were previously prepared by Kreher and Wagner[34] and recently by Bergman[35] via a new facile approach starting from indoles and cyanoacetic acid (Scheme 2).

Initially, model reaction was performed by taking 4-nitrobenzaldehyde (1; R_1 = 4-NO_2), malononitrile 2, (3-cyanoacetyl)-indole

Table 1
Effect of different surfactants on the yield of the thiamine-hydrochloride (VB_1) catalyzed reaction (Scheme 1, R_1 = 4-NO_2, R_2 = H)[a]

Entry	Surfactant	Concentration (mol %)	Time (min)	Yield (%)
1	CTAB	5	30	86
2	CTAB	10	25	92
3	SDS	10	45	64
4	TTAB	10	38	65

[a] Reaction conditions: VB_1 (5 mol %), 4-nitrobenzaldehyde (1 mmol) + malononitrile (1 mmol) + cyanoacetyl indole (1 mmol) + ammonium acetate (3 mmol) at 57 °C.

Table 2
Optimization of concentration of catalyst thiamine-hydrochloride (VB_1) for the reaction (Scheme 1, R_1 = 4-NO_2, R_2 = H)[a]

Entry	Catalyst conc. (mol %)	Time (min)	Yield[b] (%)
1	0	30	35
2	3	25	70
3	5	25	92
4	5	25	85, 80[c]
5	10	25	92

[a] Reaction conditions: catalyst + 4-nitrobenzaldehyde (1 mmol) + malononitrile (1 mmol) + cyanoacetyl indole (1 mmol) + ammonium acetate (3 mmol), in CTAB-H_2O (10 mol % in 10 ml) at 57 °C.
[b] Isolated yields after recrystallization.
[c] Yields of products with recycled catalyst in 2-successive runs.