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Green synthesis of imidazo[1,2-*a*]pyridines using calix[6]arene-SO_3H surfactant in water

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ABSTRACT

In this research, green synthesis of imidazo[1,2-*a*]pyridines in the presence of calix[*n*]arenes-SO_3H as a Brønsted acid catalyst and surfactant is described. Using of calix[*n*]arenes in water provided a hydrophobic cavity that successfully carried out the synthesis reactions at short times with high yields. This catalyst system is recoverable with a simple extraction using an organic solvent and reusable for at least for 5 cycles without any losses of its activity.

Introduction

Imidazopyridines are considered as important class of fused heterocyclic compounds possessing interesting biological and pharmacological properties as antiviral,[5] antifungal,[1] anti varicella-zoster,[2] antibacterial[4] and anti-cancer agents.[6] Specifically, imidazo[1,2-*a*]pyridine framework has been found in several marketed drugs such as Olprinone (heart failure drug),[7] Alpidem (a nonsedative anxiolytic agent),[8] Zolimidine (treatment of peptic ulcers)[9] and Zolpidem (treatment of insomnia).[8,10]

Up to now, various methods have been utilized for the synthesis of imidazo[1,2-*a*]pyridine scaffold. In this context, Groebke–Blackburn–Bienaymé (GBB) multicomponent reaction is one of the simplest synthesis routes of this important class of heterocyclic systems.[11] This reaction is based on the condensation of 2-aminoazine, an aldehyde and an isocyanide in the presence of Lewis acids like $ZnCl_2$,[12] $Sc(OTf)_3$,[13] $ZrCl_4$,[14] $MgCl_2$,[15] $RuCl_3$,[16] $LaCl_3$,[17] and Brønsted acids like cellulose sulfuric acid,[11] AcOH,[18] $HClO_4$,[11c] 4-toluene sulfonic acid.[19] Moreover, the GBB reaction has been carried out under solvent-free[20] or microwave irradiation conditions.[21] However, many of these methods suffer from some drawbacks, such as the use of toxic or expensive reagents, long reaction times, tedious work-up procedures, low yields, requirement for an inert atmosphere, and in some cases harsh reaction conditions. Thus, the development of an efficient and convenient method for the synthesis of imidazo[1,2-*a*]pyridines would be valuable.

The development of organic reactions in water has been of considerable interest in organic synthesis, because of the many advantageous properties of water as an environmentally friendly and nontoxic reaction medium. The main disadvantage of water as a solvent is that many organic compounds are hydrophobic and insoluble in water. However, the use of water-soluble supramolecular catalysts in aqueous reaction systems can potentially overcome this issue.[22–25] Calix[*n*]arenes, are a class of macrocyclic molecules, which have been used extensively as supramolecular catalysts.[26] Specifically, *p*-sulfonic acid calix[*n*]arenes showed to be the most efficient catalysts for different multicomponent reactions such as Mannich-type,[27,28] Povarov[24,25] and Biginelli.[29]

Herein we report an efficient and straightforward method for synthesis of 3-amino-imidazo[1,2-*a*]pyridines *via* the GBB three-component reaction protocol in the presence of sulfonated calix[*n*]arenes ($n = 4$ or 6) in water. The sulfonated calix[*n*]arenes as water soluble organocatalyst provide a new green catalyst system to accelerate the GBB reaction. From environmental point of view, using water as solvent in the organic transformations simplify the experimental and reaction workup in compared to reactions utilizing organic solvent and also decrease the waste and handling costs (Scheme 1).

Results and discussion

In our efforts to design a green and facile method for synthesis of imidazo[1,2-*a*]pyridines based on sulfonated calix[*n*]arenes as

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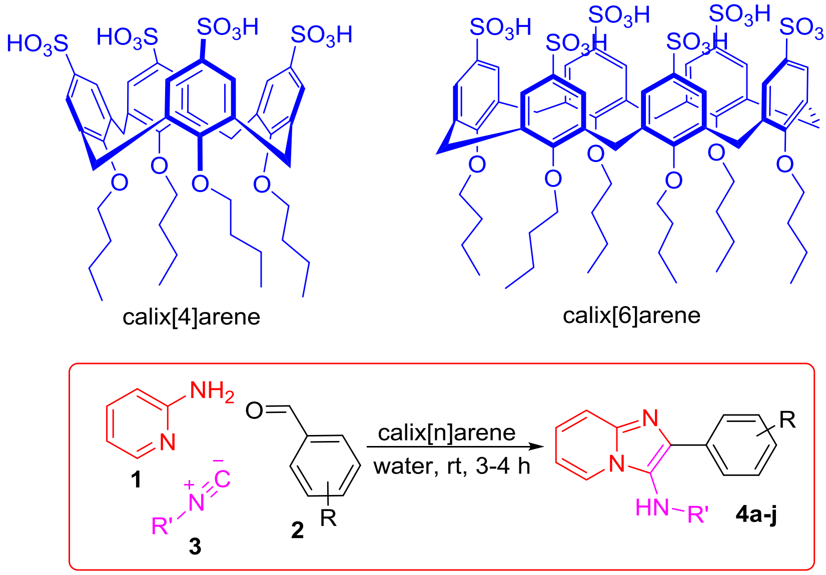
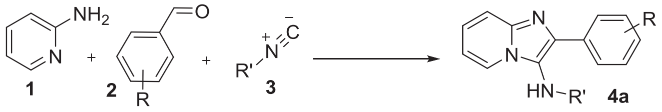


Scheme 1. Synthesis of the imidazo[1,2-*a*]pyridines in the presence of calix[*n*]arenes.

Table 1
Optimization of the reaction conditions[a].



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield[b]
1	calix[4]arene (10)	Water	25	3	38
2	calix[6]arene (10)	Water	25	3	88
3	calix[6]arene (10)	Water	50	3	90
4	calix[6]arene (10)	Water	100	4	24
5	calix[6]arene (5)	Water	25	3	51
6	calix[6]arene (15)	Water	25	3	90
7	PTSA (20)	water	25	10	28
8	calix[6]arene (10)	Ethanol	25	3	57
9	calix[6]arene (10)	Acetonitrile	25	3	46

[a] Reaction condition: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.1 mmol) and solvent (10 mL).

[b] Isolated yield.

catalyst, the reaction of 2-aminopyridine, benzaldehyde and cyclohexyl isocyanide was chosen as model reaction and water as the greenest solvent for initial investigation. As seen in the Table 1, the model reaction was examined using 0.1 equivalent of calix[4]arene and calix[6]arene in water in different temperatures that the desired product *N*-cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine **4a** was formed with 38% and 88% yields at room temperature, respectively. There was a question "what is the difference between the sulfonated calix[4]arene and calix[6]arene?". We found the best answer based on the previous report on the catalytic activity of calix[*n*]arenes for alkylation of alcohols in water, which sulfonated calix[*n*]arenes provide hydrophobic cavity in water as the surfactants, and calix[6]arene is the most effective surfactant.[30] Accordingly, It can be concluded that calix[*n*]arenes have a doul roles as Brønsted acid and surfactant. When the calix[*n*]arenes were used as a catalyst, the reaction was carried out in the hydrophobic cavity under high microscopic temperature and pressure, which the calix[6]arene provide hydrophobic cavity more effective than calix[4]arene. In order to prove the surfactant role of the calix[*n*]arenes, the *para*-toluene sulfonic acid (PTSA) was used in the model reaction under same reaction conditions, and the desired product **4a** was synthesized with 28% yield. These results confirmed that the reaction was accelerated in the hydrophobic cavity. As complementary study, the model reaction was examined with different amount of the calix[6]arene in water and in two various solvents such as ethanol and acetonitrile (see Table 1). In the cases of organic solvent, **4a** was formed with low yields. Finally, the calix[6]arene, water and room temperature were chosen as best catalyst, solvent and temperature, respectively.

With the optimized conditions in hand, scope and generality of the reaction were investigated using three derivatives of