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Novel synthesis of tetrahydro-β-carbolines and tetrahydroisoquinolines via three-component reaction using hexagonally ordered mesoporous AlSBA-15 catalysts

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ABSTRACT

Tryptamine, aryl aldehyde, and benzyl chloride undergo smooth coupling using well-ordered mesoporous AlSBA-15 catalyst with hexagonal porous structure in acetonitrile at 80 °C to furnish tetrahydrocarbolines in good yields with a high selectivity. This reaction also proceeds with homoveratrylamine to give the corresponding tetrahydroisoquinolines. A variety of aryl and heteroaryl aldehydes have also been used for producing tetrahydrocarbolines in high yields. This AlSBA-15-promoted Pictet–Spengler reaction provides a mild alternative to the traditional Brönsted or Lewis acids typically employed for the preparation of tetrahydrocarbolines and tetrahydroisoquinolines.

1. Introduction

The tetrahydro-β-carboline ring is frequently found in various natural products and synthetic pharmaceuticals displaying a wide range of biological activities.[1] The Pictet–Spengler reaction is one of the powerful synthetic routes for the preparation of tetrahydroisoquinolines and β-carbolines.[2] Typically, strong Brønsted acids have been utilized to accomplish this reaction.[3] Lewis acid-catalyzed Pictet–Spengler reactions have also been reported in the literature.[4] Generally, activated substrates containing a catechol functionality undergo Pictet–Spengler reactions under mildly acidic conditions whereas less activated substrates such as tryptamine and tryptophan provide low conversions (vide infra).[5] Homogeneous catalysts such as chiral thiourea, (*S*)-BINOL phosphoric acid, molecular iodine, and TFA/H_2O have recently been used for this conversion.[6,7] Unfortunately, the use of the above catalysts in the industry triggers a lot of environment-related issues as they are highly corrosive in nature and cannot be regenerated for further use. In addition, tedious work-setup is required for treating the large quantities of metal salt wastes. To avoid the above environmental-related problems, it is desirable to develop a catalyst process which is heterogeneous, stable, environmentally friendly, and recyclable. Recently, mesoporous molecular sieves have attracted significant attention in the field of adsorption, catalysis, and separation as they exhibit excellent textural characteristics such as a high surface area, a large pore volume, and a narrow pore size distribution. In addition, they are highly efficient, sustainable, recyclable, and eco-friendly. SBA-15 mesoporous material has been synthesized under acidic condition using a triblock copolymer as a structure-directing agent. This novel mesoporous material has opened a new window in the field of catalysis and material science owing to its significant properties such as thick pore walls and tunable pores. Moreover, the wall thickness and pore diameter of the SBA-15 are larger than those of the MCM-41 which is synthesized by highly expensive cationic surfactant in a highly basic medium.[8] These superior properties of SBA-15 make them more suitable to deal with the reaction between the bulky molecules or multi-component reactions.[9] However, pure mesoporous silica is neutral in charge and offers only mild acidity which limits its application in catalysis. Thus, the incorporation of Al and other trivalent metals into the amorphous silica walls is mandatory for the formation of catalytically active sites.[10,11] The incorporation of aluminum into SBA-15 by post-synthetic and direct methods has been established.[12] Recently, we have reported the successful direct synthesis of aluminum substituted SBA-15 (AlSBA-15) materials with a high aluminum content and tunable pore diameters by simply adjusting the molar water to

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hydrochloric acid ratio ($nH_2O/nHCl$)[13] and found better performances in the *tert*-butylation of phenol as compared with that of AlMCM-41, sulfated zirconia, and FeAl–MCM-41.[14] Although AlSBA-15 possesses a large pore diameter, unfortunately, only the reaction involving the transformation of small molecules inside the pore channels of AlSBA-15 has been conducted so far.

2. Results and discussion

Herein we demonstrate for the first time the Pictet–Spengler reactions of tryptamine with aryl aldehydes in the presence of benzyl chloride using highly ordered mesoporous AlSBA-15 with hexagonal pore structure as a catalyst (Scheme 1).

The reaction was carried out in a single-step operation. Initially, the effect of the solvents including acetonitrile, ethanol, 1,4-dioxane, 1,2-dichloroethane, toluene, and THF on the reaction has been studied over AlSBA-15 catalyst. Among the solvents studied, acetonitrile was found to be the best solvent for the catalytic reaction. The reactions proceeded smoothly at 80 °C and the desired products were obtained in good yields after 4–8 h. The results presented in Table 1 clearly show that all the studied aldehydes participated in Pictet–Spengler reactions with tryptamine in short reaction times affording good yields of products. The optimized conditions were subsequently applied to several other aldehydes (Table 1). When compared to other methods for the synthesis of tetrahydro-β-carbolines, the solid acid-induced reaction tolerates the sensitive indole unit well. Another interesting feature of this method is that aryl aldehydes bearing either electron-withdrawing or electron-donating groups successfully underwent the Pictet–Spengler reaction with equal ease. Tryptamine was reacted with various aldehydes in the presence of a catalytic amount of AlSBA in acetonitrile to produce tetrahydro-β-carbolines in short reaction times. Encouraged by the results obtained with tryptamine, we extended our protocol to veratrylamine, which is known to be a less reactive substrate than tryptamine, toward Pictet–Spengler reaction using our highly active AlSBA-15 catalyst. Interestingly, veratrylamine also participated effectively in Pictet–Spengler reaction to furnish the tetrahydroisoquinoline **4l** in good yield (Table 1, entry l, Scheme 2).

It should be mentioned that the yield of the products is in the range of 50–70% though the aldehyde molecules are converted completely in the reaction. This could be mainly due to the fact that the reaction of benzyl chloride with amine may produce HCl as a by-product, which subsequently reacts with carboline resulting in the formation of carbolinehydrochloride. Therefore, the product might have lost in work-up due to its high solubility in water. Another reason is that carbolines might be binding with silica while purification. Therefore, we can expect some product loss on silica gel column. Noteworthy, we have not observed any byproduct formation by TLC under present reaction conditions.

Next, we have attempted the Pictet–Spengler cyclization between *m*-tyramine (3-hydroxyphenethyl amine) and aldehydes under similar conditions. Interestingly, both electron-rich and electron-deficient aldehydes participated well in this reaction to furnish hydroxyl-substituted tetrahydroisoquinolines in good yields. In the absence of benzyl chloride, the reaction was sluggish as has been observed by Cook and co-workers.[15] This may be attributed to the low electrophilicity of the imine which might be enhanced by activation with benzyl chloride. Similarly, in the absence of catalyst, the resulting iminium ion (formed in situ from imine and benzyl chloride) failed to undergo Friedal–Crafts-type cyclization to give the desired product. The presence of both the catalyst and benzyl chloride is essential to accomplish the reaction. Mechanistically, the reaction proceeds via the formation of imine from amine and aldehyde followed by iminium ion resulting from benzyl chloride and imine. This iminium ion may undergo Friedal–Crafts-type cyclization to provide the desired carboline (Scheme 3).[15]

Finally, we have examined the efficiency of solid acid catalysts with different structure and aluminum contents in different solvents in the preparation of product **4c**. Among them, AlSBA-15 (6.6) where the number in the parenthesis denotes the Si/Al ratio was found to be the best in terms of conversion. As solvent, acetonitrile appears to give high conversions and the results are presented in Table 2. The higher activity of the AlSBA-15(6.6) could be due to its high acidity, well-ordered pore structure, and excellent textural characteristics.[13,14]

The advantage of the use of AlSBA-15 is that it can be easily recovered and recycled in subsequent runs. After complete disappearance of aldehyde as indicated by TLC, the reaction mixture was centrifuged to separate the catalyst. Thus recovered catalyst was further washed with ether, dried at 120 °C under reduced pressure, and reused in three to four successive runs with only a minimal decrease in activity and the results are presented in Table 3. The small decrease in the activity after the repeated reaction cycles could be due to either the blockage of the active sites by the product molecules or the slight deterioration of the structural order of the materials.

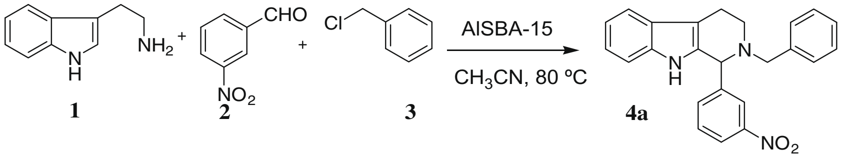
In summary, we have developed a novel, convenient, and simple one-pot procedure for the synthesis of tetrahydro-β-carbolines and tetrahydroisoquinolines using AlSBA-15. This method provides a mild alternative to the typical conditions requiring strong Brønsted acids.

3. Experimental section

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. ^1H NMR and ^{13}C spectra were recorded on JEOL AL-300/BZ spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra (MS) were measured by using AXIMA-CFR, Shimadzu/Kratos TOF Mass spectrometer. Column chromatography was performed using E. Merck 60–120 mesh, silica gel.

3.1. General procedure

A mixture of aldehyde (1 mmol), tryptamine (1 mmol), benzyl chloride (1 mmol), and AlSBA-15 (20 mg) in acetonitrile (2 mL) was stirred at 80 °C for the specified amount of time (Table 1).



Scheme 1. Synthesis of tetrahydrocarboline **4a** using AlSBA-15.

Table 1
Synthesis of tetrahydrocarbolines using A1SBA-15 in 1,4-dioxane

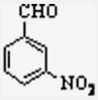
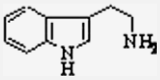
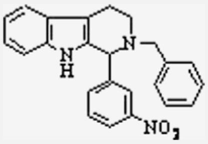
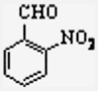
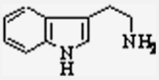
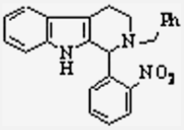
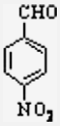
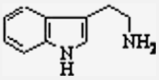
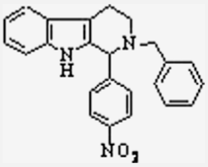
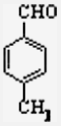
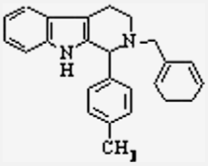
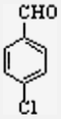
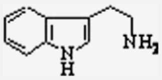
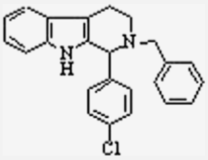
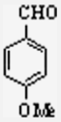
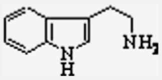
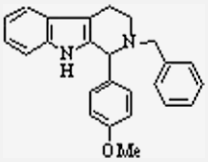
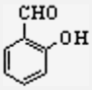
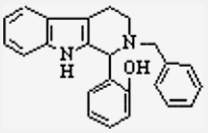
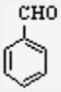
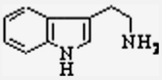
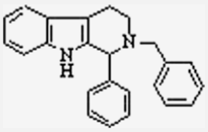
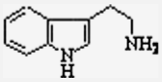
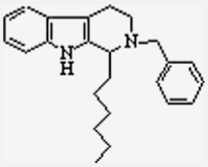
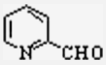
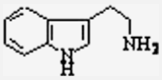
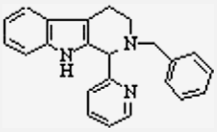
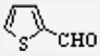
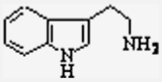
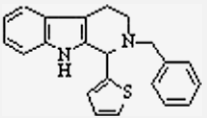
Entry	Aldehyde	Amine	Time (h)	Product	Yield (%)
a			9.0		70
b			9.0		73
c			9.0		76
d			7.0		72
e			8.0		75
f			7.0		77
g			10.0		61
h			9.0		70
i			9.0		79
j			8.0		58
k			8.0		81

Table 1 (*continued*)

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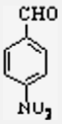
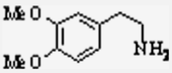
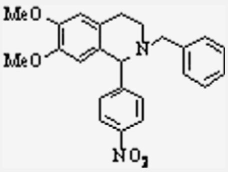
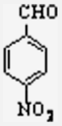
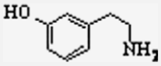
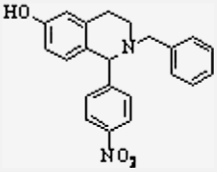
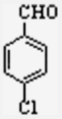
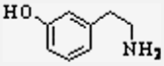
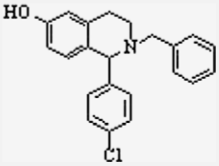
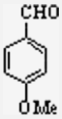
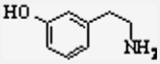
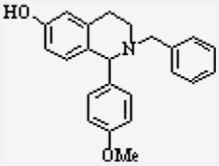
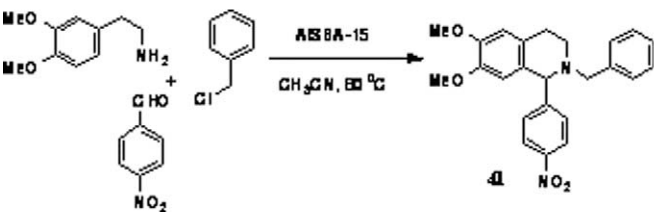
l			12.0		55
m			12.0		78
n			12.0		79
o			12.0		75



Scheme 2. Synthesis of tetrahydroisoquinoline **4l** using AlSBA-15 catalyst.

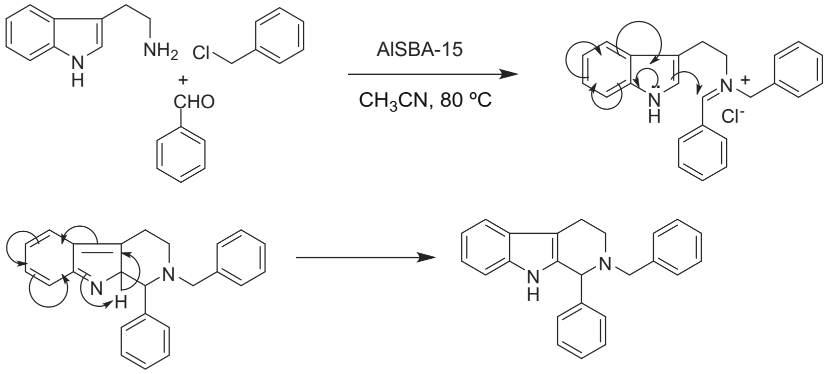
After complete disappearance of aldehydes as indicated by TLC, the reaction mixture was centrifuged to separate the catalyst. The resulting supernatant liquid was concentrated under reduced pressure and the crude product was purified by column chromatography using silica gel (60–120 mesh, ethyl acetate–hexane, 1:3) to give the desired product. The product thus obtained was characterized by NMR and MALDI mass spectroscopy. The spectral data of the product were found to be consistent with those of the authentic sample.[3–7]

Table 2
Synthesis of tetrahydro-β-carbolines using various catalysts and solvents

Entry	Catalyst	Solvent	Yield (%)
1	A1-KITS (3.3)	MeCN	65
2	A1SBA-15 (6.6)	MeCN	76
3	A1-KITS (3.3)	EtOH	48
4	A1SBA-15 (6.6)	EtOH	56
5	A1SBA-15 (6.6)	1,4-Dioxane	73
6	A1SBA-15 (6.6)	1,2-Dichloroethane	70
7	A1SBA-15 (6.6)	Toluene	65
8	A1SBA-15 (6.6)	THF	48

Table 3
Reusability of the catalyst in the preparation of **4a**

Entry	Number of cycles	Time (h)	Yield (%)
1	1st cycle	9.0	70
2	2nd cycle	10.0	75
3	3rd cycle	12.0	71
4	4th cycle	13.0	65



Scheme 3. Mechanism of the formation of tetrahydro-β-carbolines using AlSBA-15 catalyst.

Acknowledgments

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References and notes

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