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Immobilized Ionic Liquid-Catalyzed Synthesis of Pyrano[3,2-*b*]indole Derivatives

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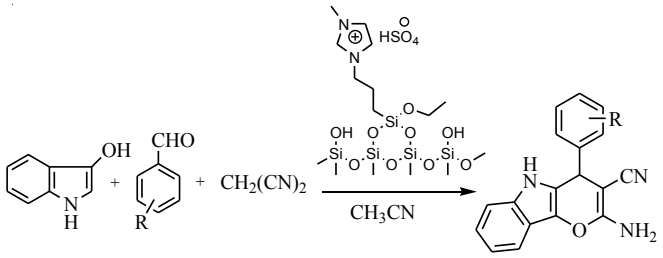
Abstract: An ionic liquid-catalyzed synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives through a novel three-component condensation of 3-hydroxyindole, aromatic aldehydes and malononitrile in the presence of silica supported ionic liquid of [pmim]HSO_{4SiO2} (silica supported 1-methyl-3-(triethoxysilylpropyl) imidazolium hydrogensulfate) as an efficient catalyst is described.

Keywords: multicomponent, 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles, hydrogensulfate ionic liquid.

Introduction

Ionic liquids have recently become a powerful alternative to conventional molecular organic solvents due to their particular properties, such as undetectable vapor pressure and the ability to dissolve many organic and inorganic substances.[1] Among these ionic liquids possessing HSO_4^- as a counteranion find a broad application in organic synthesis, acting as both solvents and catalysts. Recently, immobilization processes involving acidic ionic liquids on solids supports have been designed.[2-5] The heterogenization of catalysts and reagents can offer important advantages in handling, separation and reuse procedures. Based on economic criteria, it is desirable to minimize the amount of ionic liquid utilized in a potential process. Immobilized acidic ionic liquids have been used as novel solid catalysts for a wide range of reactions.[6-10]
The anticancer potential of indole and α-pyrone derivatives have been reported already. [11,12]. Accordingly, due to their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical harmaceuticals,[13] a number of synthetic methods have been developed in pursuit of this structure, including intramolecular hetero-Diels-Alder cycloaddition[14] and cycloisomerization. Moreover, based catalyzed one-pot synthesis of pyrano[3,2-*b*]indoles has been reported by our research group.[15]

In continuation of our effort toward the development of new multi-component condensation reactions,[16] herein, we wish to report an efficient methodology for the preparation of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives through a three-component condensation reaction of indolin-3-one, aryl aldehydes, and malononitrile catalyzed by silica supported ionic liquid of [pmim]$HSO_{4\ SiO2}$ (silica supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogensulfate) (Figures 1).



Ar = 4-$CH_3OC_6H_4$ - (**1**)(84%); C_6H_5 - (**2**)(90%); 4-$CH_3C_6H_4$ (**3**)(85%); 4-BrC_6H_4 (**4**)(90)
;
2-BrC_6H_4 - (**5**)(86%); 4-ClC_6H_4 (**6**)(90%); 2-ClC_6H_4 - (**7**)(86%); 4-$CH_3C_6H_4$ - (**8**)(90%)

; 4-$NO_2C_6H_4$ - (**9**) (85); 2-$NO_2OC_6H_4$ - (**10**)(88%).

Figure 1. Synthesis of pyrano[3,2-*b*]indole derivatives **1-10.**

Experimental

All the compounds are known and have been reported recently.[15] [pmim]$HSO_{4\ SiO2}$ (extent of labeling 0.25 mmol/gr loading) was prepared according to the literature.[17]

*General Procedure for synthesis of pyranopyrrole derivatives **1-10***

A mixture of aldehyde (1 mmol), 3-hydroxyindole (1 mmol), malononitrile (1.1 mmol) and ionic liquid catalyst (0.1 mmol) in CH_3CN (8 mml) was stirred at 80 °C for the appropriate time (6-8 h). The reaction was monitored by TLC and after completion of the reaction, the catalyst was simply recovered by filtration and washed by dichloromethane. The residue was concentrated in *vacuo* and the crude product was purified by column chromatography on silica gel eluting by *n*-hexane/ethyl acetate (9:1).

Entry 1. IR: 1665 (NH_2), 2218 (-CN), 3224 & 3259 (asym. & sym. str. of -NH_2). ^{1}H NMR: δ_H 3.63 (s, 3H, OCH_3), 5.41 (s, 1H, CH), 6.89 (bs, 2H, NH_2), 6.82-6.99 (m, 2 H); 7.04-7.13 (m, 4 H); 7.56 (d,1 H, J = 8.0); 7.87 (d, 1 H, J = 7.8), 10.14 (bs, 1H, NH). Anal Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24 %. Found: C, 71.75; H, 4.67; N, 13.11 %.
Entry 4. IR: 1670 (NH_2), 2226 (-CN), 3240 & 3361 (asym. & sym. str. of -NH_2). ^{1}H NMR: δ_H: 5.50 (s, 1H, CH), 6.70 (bs, 2 H, NH_2), 7.07-7.16 (m, 2 H); 7.30-7.44 (m, 4 H); 7.68 (d, 1 H, J = 7.6); 8.01 (d, 1 H, J = 7.0), 11.02 (bs, 1H, NH). Anal Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47 %. Found: C, 58.76; H, 3.27; N, 11.40 %.
Entry 6. IR: 1667 (NH_2), 2219 (-CN), 3202 & 3244 (asym. & sym. str. of -NH_2). ^{1}H NMR: δ_H 5.49 (s, 1H, CH), 6.68 (s, 2H, NH_2), 7.21-7.42 (m, 2 H); 7.46-7.59 (m, 4 H); 7.63 (d, 1 H, J = 6.7); 8.01 (d, 1 H, J = 7.0), 10.54 (bs, 1H, NH). Anal Calcd for $C_{18}H_{12}ClN_3O$: C, 70.81; H, 3.96; N, 13.76 %. Found: C, 70.55; H, 3.90; N, 13.71 %.
Entry 9. IR: 1669 (NH_2), 2225 (-CN), 3218 & 3231 (asym. & sym. str. of -NH_2). ^{1}H NMR: δ_H 5.72 (s, 1H, CH), 6.71 (s, 2H, NH_2), 7.22 (d, 1 H, J = 7.76); 7.26-7.42 (m, 3 H); 7.46-7.59 (m, 2 H); 7.76 (d, 1 H, J =7.6); 7.99 (d, 1 H, J = 6.9), 10.11 (bs, 1H, NH). Anal Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.64; N, 16.86 %. Found: C, 64.86; H, 3.53; N, 16.75 %.
Entry 10. IR: 1661 (NH_2), 2200 (-CN), 3224 & 3262 (asym. & sym. str. of -NH_2). ^{1}H NMR: δ_H 5.11 (s, 1H, CH), 6.75 (bs, 2H, NH_2), 7.12-7.29 (m, 4 H); 7.38-7.52 (m, 2 H); 7.63 (d, 1

H, *J* = 7.1); 8.20 (d, 1 H, *J* = 8.01), 10.24 (bs, 1H, NH). Anal Calcd for $C_{18}H_{12}FN_3O$: C, 70.81; H, 3.96; N, 13.76 %. Found: C, 70.56; H, 3.91; N, 13.68 %.

Results and Discussion

Induced by significant advantages such as ease of separation from reaction mixture, significant reduction in problems of waste disposal, and re-use applications by recycling, [pmim]HSO_4, was supported on the modified silica to obtain the immobilized catalyst of [pmim]HSO_{4Sio2} (Figure 1). The reaction of 3-hydroxypyrrole (1.0 equiv.), benzaldehyde (1.0 equiv.), malononitrile (1.0 equiv.) and 10 mol% of [pmim]$HSO_{4\ SiO2}$, using 8 mL of acetonitrile at 80 °C was chosen as the model reaction and the corresponding product (**2**) was obtained in 90% yield. Furthermor, the supported catalyst underwent only negligible loss in its activity even after at least three recycles (Table 1).

Table 1. Reusability of [pmim]$HSO_{4\ SiO2}$ [a].

No. of Run	1	2	3	4	5
Yield	90	87	85	85	82

[a] Reaction conditions: 1.0 equiv. of 3-hydroxypyrrole, 1.0 equiv. of benzaldehyde, 1.0 equiv. of malononitrile, 10 mol% of [pmim]$HSO_{4\ SiO2}$, 8 mL of solvent and at 80 °C.

We then successfully synthesized a variety of pyrano[3,2-*b*]indole derivatives and the results were summarized in Figure 1. As shown, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently giving good to excellent yields of the corresponding pyrano[3,2-*b*]indoles.

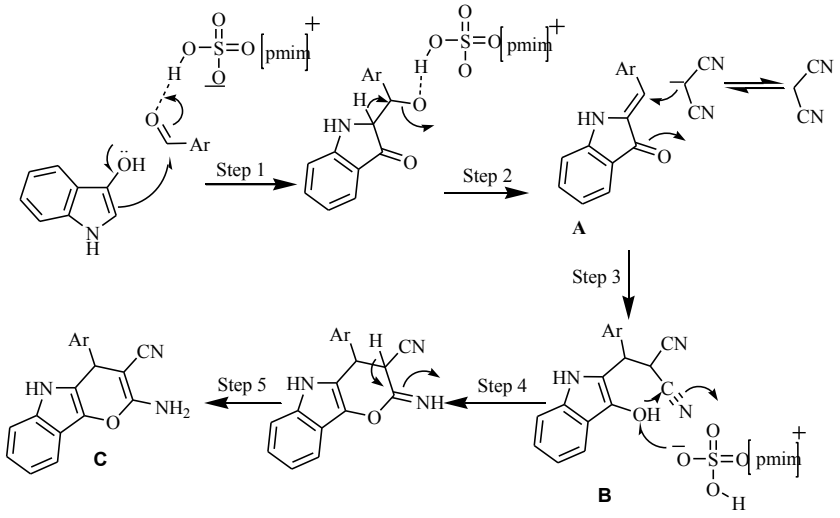


Figure 2. The proposed mechanism.

The proposed mechanism for the synthesis of pyrano[3,2-*b*]indoles is shown in Figure 2. The condensation of 3-hydroxyindole, arylaldehyde and malononitrile may occur by a mechanism of Knoevenagel condensation, Michael addition, intramolecular cyclization, and isomerization. Initially, by the aid of [pmim]$HSO_{4\ SiO2}$, intermediate **A** is formed through condensation of 3-hydroxyindole and aromatic aldehyde. Michael-type addition of

malononitrile to the intermediate **A** gives **B**. Then, the proton of **B** is abstracted by counteranion of HSO_4^- followed by heterocyclization and isomerization to furnish the corresponding pyrano[3,2-*b*]indole product **C** (Figure 2).

Conclusion

In conclusion, we developed a novel, mild and effective one-pot method for the synthesis of substituted pyrano[3,2-*b*]indole-3-carbonitrile derivatives utilizing silica supported ionic liquid of $[pmim]HSO_{4\ SiO2}$.

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