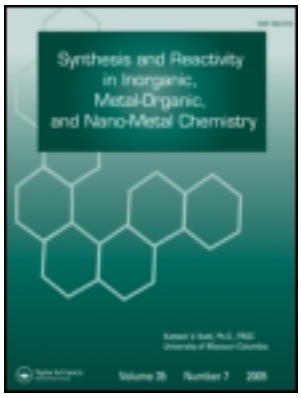

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

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Novel Synthetic Route to Pyrano[2,3-b]pyrrole Derivatives

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Novel Synthetic Route to Pyrano[2,3-*b*]pyrrole Derivatives

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Synthesis of a new series of 2-amino-4,7-dihydro-4-arylpyrano[2,3-*b*]pyrrole-3-carbonitrile has been reported. The acid-catalyzed cyclocondensation synthesis proceeded by the one-pot reaction of 2-hydroxypyrrole, malononitrile, and various aromatic aldehydes in the presence of silica-supported ionic liquid of [pmim]$HSO_{4\,SiO2}$ (silica-supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogensulfate) as an efficient catalyst. The electronic nature of the substitution attached to the aldehyde affected the reaction efficiency profoundly.

Keywords 2-amino-4, 7-dihydro-4-arylpyrano[2,3-*b*]pyrrole-3-carbonitrile, hydrogensulfate ionic liquid, one-pot

INTRODUCTION

Recently, ionic liquids have 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] In addition, the ionic liquids are readily recycled and tunable to specific chemical tasks. One type is Brønsted acidic task-specific ionic liquids (BAILs). Among these ionic liquids possessing HSO_4 as a counteranion they 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.[2–8] 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 spectrum of reactions.[9–13]

The *4H*-pyran derivatives are of the immense interests in the area of synthesizing veracious drugs due to their various pharmacological and biological activities, such as antimicrobial,[14] mutagenicity,[15,16] antiproliferative,[17] sex pheromone,[18] antitumor,[19] cancer therapy,[20–22] and central nervous system activity.[23] Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals.[24] Accordingly, the synthesis of such compounds is an interesting challenge.

Many researches have been devoted to the synthesis of various pyran derivatives such as benzopyrans,[25,26] naphtopyrans,[27–29] and 4-substitueted pyrans[30] in order to the obtain more biologically potent heterocyclic systems. However, to the best of our knowledge, synthesis of 2-amino-4,7-dihydro-4-arylpyrano[2,3-*b*]pyrrole-3-carbonitrile derivatives has never been reported up to now. In the present study, we have reported the synthesis of 2-amino-4,7-dihydro-4-arylpyrano[2,3-*b*]pyrrole-3-carbonitrile by one-pot cyclocondensation of 3-hydroxypyrrole, aromatic aldehydes, and malononitrile in the presence of [pmim]HSO_{4SiO2} being a silica-supported ionic liquid with acidic counteranion of HSO_4^- (Figures 1 and 2).

EXPERIMENTAL

General

All chemicals and accessible ionic liquids were purchased from Merck, Fluka, and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by their spectral data. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker. 100-MHz spectrometer in chloroform as the solvent and TMS as internal standard. Elemental analysis (C, H, N%) was carried out by Perkin-Elmer 2400 series-II elemental analyzer. [pmim]$HSO_{4\,SiO2}$ (extent of labeling 0.25 mmol/gr loading) was prepared according to the literature.[31]

General Procedure for Synthesis of Pyranopyrrole Derivatives 5a-l

A mixture of aldehyde (1 mmol), 2-hydroxypyrrole (1 mmol), malononitrile (1.1 mmol), and ionic liquid catalyst (0.1 mmol) in CH_3CN (4 mml) was stirred at 60°C for the appropriate time. 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.

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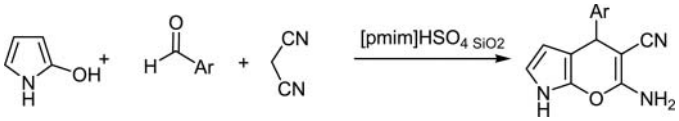


FIG. 1. One-pot synthesis of pyranopyrroles.

2-amino-4,7-dihydro-4-(4-methoxyphenyl)pyrano[2,3-b]pyrrole-3-carbonitrile ***(5a)***

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%. Found: C, 66.31; H, 4.81; N, 15.63%. IR (KBr, ν_{max}, cm^{-1}): 3410 & 3255 (asym. & sym. str. of -NH_2), 3400 (NH), 2120 (-CN str.), 1265 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 3.55 (s, 3H, OCH_3), 5.58 (s, 1H, CH), 6.17 (d, 1H, pyrr), 6.55 (d, 2H, Ar-H), 6.65 (d, 1H, pyrr), 6.97 (s, 2H, D_2O exch., NH_2), 7.12 (d, 2H, Ar-H), 7.64 (s, 1H, pyrrole NH). ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 28.2, 61.11, 63.15, 101.7, 106.9, 119.9, 122.5, 126.7, 120.2, 127.7, 129.9, 154.1, 167.4.

2-amino-4,7-dihydro-4-p-tolylpyrano[2,3-b]pyrrole-3-carbonitrile ***(5c)***

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72%. Found: C, 70.86; H, 5.11; N, 16.55%. IR (KBr, ν_{max}, cm^{-1}): 3411 & 3265 (asym. & sym. str. of -NH_2), 3427 (NH), 2205 (-CN str.), 1275 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 2.34 (s, 3H, Ar-CH_3), 5.66 (s, 1H, CH), 6.20 (d, 1H, pyrr), 6.84 (s, 2H, D_2O exch., NH_2), 6.92 (d, 1H, pyrr), 7.03–7.12 (m, 4H, Ar-H), 7.40 (s, 1H, pyrr NH). ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 24.2, 29.10, 57.25, 102.4, 105.8, 117.4, 126.1, 133.3, 129.2, 129.7, 132.2, 141.1, 167.1.

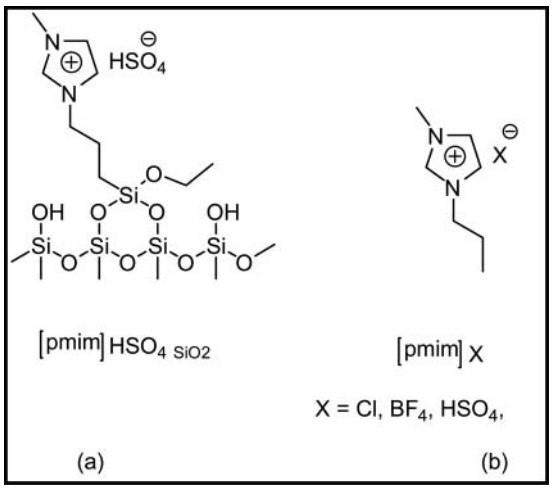


FIG. 2. Structures of silica-supported (a) and unsupported ionic liquid catalysts (b).

TABLE 1
Comparing the catalytic efficiency of various ionic liquids[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	—	24	0
2	[pmim]$HSO_{4\ SiO2}$	5	90
3	[pmim]HSO_4	8	63
4	[pmim]BF_4	7.5	15
5	[pmim]Cl	10	7

[a]Reaction conditions: 1.0 equiv. of 2-hydroxypyrrole, 1.0 equiv. of benzaldehyde, 1.0 equiv. of malononitrile, 10 mol% of catalyst, 4 mL of CH_3CN as solvent and at 60°C.
[b]Isolated yields.

2-amino-4-(4-bromophenyl)-4,7-dihydropyrano[2,3-b]pyrrole-3-carbonitrile ***(5e)***

Anal. Calcd. for $C_{14}H_{10}BrN_3O$: C, 53.19; H, 3.19; N, 13.29%. Found: C, 52.66; H, 3.15; N, 13.22%. IR (KBr, ν_{max}, cm^{-1}): 3410 & 3295 (asym. & sym. str. of -NH_2), 3405 (NH), 2175 (-CN str.), 1251 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 5.55 (s, 1H, pyrr), 6.27 (d, 1H, pyrr), 6.65 (d, 1H, pyrr), 6.85 (s, 2H, D_2O exch., NH_2), 6.95–7.20 (m, 4H, Ar-H), 7.75 (brs, 1H, pyrr NH). ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 28.7, 56.2, 110.1, 111.9, 118.6, 124.5, 126.7, 128.8, 129.7, 132.5, 133.4, 142.4, 173.4.

2-amino-4-(4-cyanophenyl)-4,7-dihydropyrano[2,3-b]pyrrole-3-carbonitrile ***(5h)***

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36%. Found: C, 67.95; H, 3.76; N, 20.98%. IR (KBr, ν_{max}, cm^{-1}): 3417 & 3235 (asym. & sym. str. of -NH_2), 3440 (NH), 2165 (-CN str.), 1245 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 5.55 (s, 1H, pyrr), 6.14 (d, 1H, pyrr), 6.53 (s, 2H, D_2O exch., NH_2), 6.71 (d, 1H, pyrr), 7.15 (s, 1H, pyrr NH), 7.22 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H). ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 32.4, 62.72, 110.1, 114.4, 121.9, 122.6, 124.8, 125.5, 129.7, 129.9, 133.5, 138.3, 172.7.

TABLE 2
Reusability of [pmim] $HSO_{4\ SiO2}$[a]

No. of run	Time (h)	Yield (%)[b]
1	3	90
2	3	88
3	3	87
4	3	84

[a]Reaction conditions: 1.0 equiv. of 2-hydroxypyrrole, 1.0 equiv. of benzaldehyde, 1.0 equiv. of malonoitrile, 10 mol% of [pmim] $HSO_{4\ SiO2}$, 4 mL of solvent and at 60°C.
[b]Isolated yields.

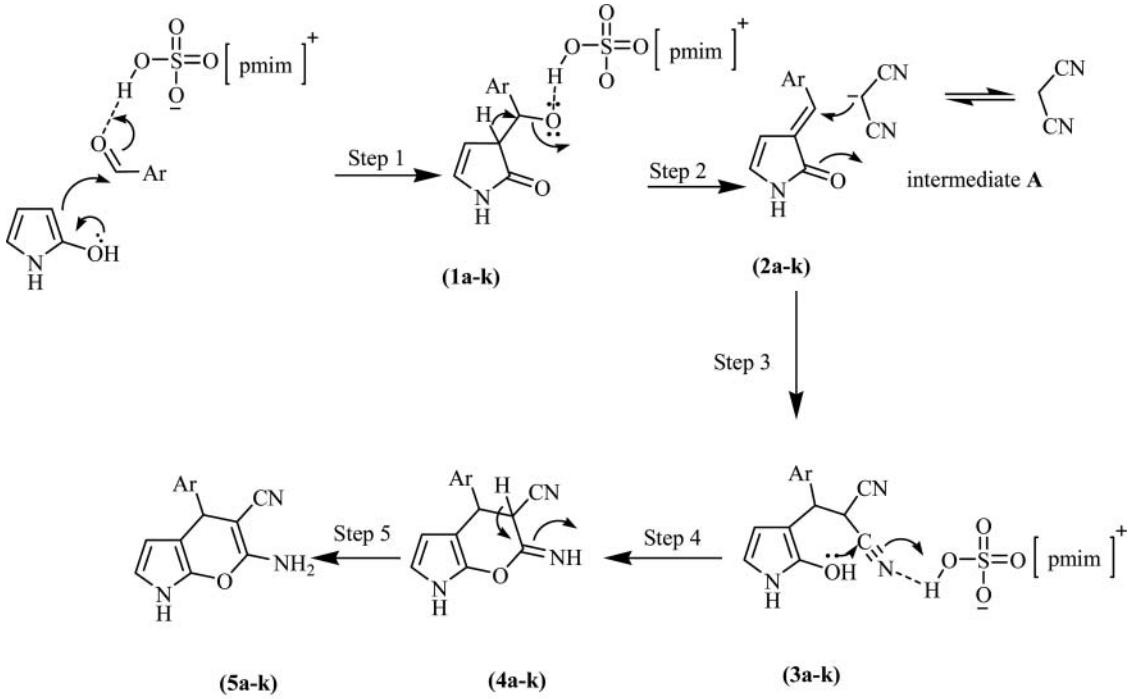
TABLE 3
Effect of solvents on the catalytic efficiency of [pmim] $HSO_{4\ SiO2}$[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Benzene	6	60
2	CH_3CN	5	90
3	MeOH	7	34
4	EtOH	6.5	55
5	Toluene	7.5	67

[a]Reaction conditions: 1.0 equiv. of 2-hydroxypyrrole, 1.0 equiv. of benzaldehyde, 1.0 equiv. of malonoitrile, 10 mol% of [pmim] $HSO_{4\ SiO2}$, 4 mL of solvent and at 60°C.
[b]Isolated yields.

2-amino-4,7-dihydro-4-(4-nitrophenyl)pyrano[2,3-b]pyrrole-3-carbonitrile ***(5j)***

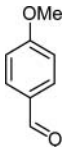
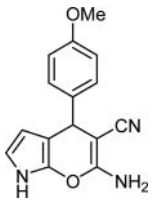
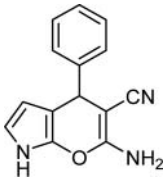
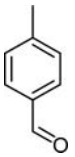
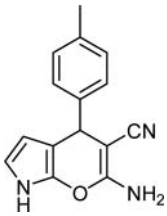
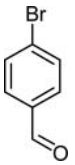
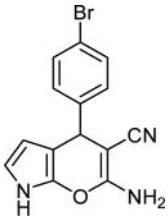
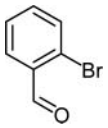
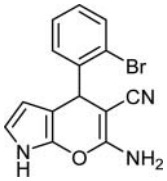
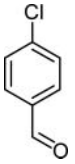
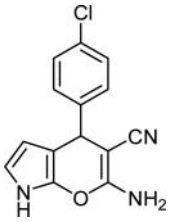
Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85%. Found: C, 59.33; H, 3.51; N, 19.74%. IR (KBr, ν_{max}, cm^{-1}): 3412 & 3225 (asym. & sym. str. of -NH_2), 3435 (NH), 2190 (-CN str.), 1355 & 1554 (asym. & sym. str. of -NO_2), 1241 (asym. str. of cyclic ArC-O-C ether). ^1H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 5.50 (s, 1H, pyrr), 6.24 (d, 1H, pyrr), 6.43 (s, 2H, D_2O exch., NH_2), 6.65 (d, 1H, pyrr), 7.35 (s, 1H, pyrr), 7.41 (d, 2H, Ar-H), 8.10 (d, 2H, Ar-H),. ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 28.8, 55.33, 105.5, 107.9, 118.3, 126.7, 128.7, 129.4, 129.6, 136.7, 143.3, 169.2.



Compnd	Ar
a	4-OMe-C_6H_4
b	C_6H_6
c	*4*-Me-C_6H_4
d	4-Br-C_6H_4
e	2-Br-C_6H_4
f	4-Cl-C_6H_4
g	2-Cl-C_6H_4
h	4-CN-C_6H_4
i	2-CN-C_6H_4
j	4-NO_2-C_6H_4
k	2-NO_2-C_6H_4
l	2-Furyl

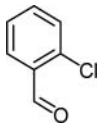
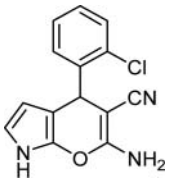
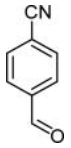
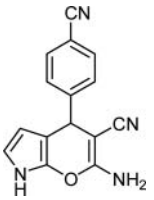
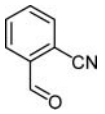
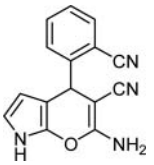
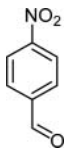
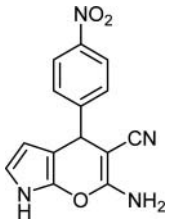
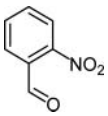
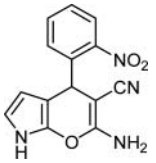
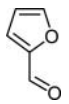
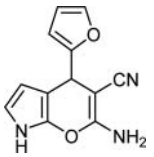
FIG. 3. Proposed mechanism for one-pot three-component synthesis of pyrano[3,2-*b*]pyrrole derivatives catalyzed by [pmim] $HSO_{4\ SiO2}$.

TABLE 4
One-pot three-component synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrroles[a]

Entry	Aldehyde	Product[b]	Time (h)	Yield (%)[c]
1			5	76
2			4	90
3			4.5	82
4			2.5	90
5			3	88
6			2	90

(continued on next page)

TABLE 4
One-pot three-component synthesis of 5-amino-7-aryl-6-cyano-4*H*-pyrano[3,2-*b*]pyrroles[a] *(continued)*

Entry	Aldehyde	Product[b]	Time (h)	Yield (%)[c]
7			2	86
8			4.5	73
9			5.5	70
10			8	64
11			8	62
12			7	40

[a]Reaction conditions: 1.0 equiv. of 3-hydroxypyrrole, 1.0 equiv. of aldehyde, 1.0 equiv. of malonoitrile, 10 mol% of [pmim] $HSO_{4\ SiO2}$, 4 mL of CH_3CN as solvent and at 60°C.

[b]The products were identified by ^{1}HNMR and IR spectrometer.

[c]Isolated yields.

2-amino-4-(furan-2-yl)-4,7-dihydropyrano[2,3-b]pyrrole-3-carbonitrile ***(5l)***

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49%. Found: C, 63.13; H, 3.89; N, 18.33%. IR (KBr, ν, cm^{-1}): 3415 & 3232 (asym. & sym. str. of -NH_2), 3425 (NH), 2166 (-CN str.), 1255 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, CD_3Cl_3) δ_H (ppm): 5.43 (s, 1H, CH), 5.85 (dd, 1H, furan), 6.27 (m, 2 H, pyrr & furan), 6.55 (d, 1H, pyrr), 6.65 (s, 2H, D_2O exch., NH_2), 7.33 (d, 1H, furan), 7.50 (s, 1H, pyrr NH). ^{13}C NMR (250 MHz, CD_3Cl_3) δ_C (ppm): 29.5, 56.7, 105.4, 107.3, 111.1, 112.9, 121.5, 126.6, 138.8, 144.3, 150.7, 163.6.

RESULTS AND DISCUSSIONS

Initially, a mixture of benzaldehyde (1 mmol), 3-hydroxypyrrole (1 mmol), and malononitrile (1 mmol), and 10% mol of different ionic liquid catalysts, was chosen as the model reaction. To find out the most effective catalyst, three ionic liquids of [pmim]HSO_4 (1-propyl-3-methylimidazolium-HSO_4), [pmim]BF_4 (1-propyl-3-methylimidazolium-BF_4), and [pmim]Cl (1-propyl-3-methylimidazolium-Cl), possessing different counteranions (Figure 2), were comparatively used for catalyzing the model reaction (Table 1, entries 3–5). As can be seen in Table 1, among the used ionic liquid catalysts, [pmim]HSO_4 showed better catalytic efficiency (entry 3).

Induced by significant advantages, such as ease of separation from reaction mixture, significant reduction in problems of waste disposal, and reuse applications by recycling, many efforts have been devoted by many researcher groups for the preparation of supported catalysts in the area of transition metal catalyst mediated various organic reactions in the past decades.[32–34] Therefore, among the prepared catalysts, the highest active one, [pmim]HSO_4, was supported on modified silica to obtain the immobilized catalyst of [pmim]HSO_{4Sio2} (Figure 2). Immobilization on silica slightly enhanced activity of the corresponding catalyst and surprisingly shortened the reaction time (Table 1, entry 2). Additionally, supported catalyst underwent only negligible loss in its activity even after at least three recycles (Table 2).

To investigate the effect of solvent on the catalytic efficiency of [pmim]$HSO_{4\ SiO2}$, various solvents were examined for the model reaction (Table 3). Protic solvents such as ethanol and methanol afforded poor results. Inversely, application of polar aprotic solvent such as acetonitrile significantly improved chemical yields and reaction times. Moreover, moderate yields were obtained using toluene and benzene as apolar media for the model reaction.

According to the recent literatures that have shown *ortho*-quinone methides (OQMs) as *in situ* intermediate in one-pot three-component synthesis of naphtopyran derivatives.[35,36] we herein envisioned a mechanism with similar intermediate (intermediate **A**) for one-pot three-component synthesis of pyranopyrrole derivatives (Figure 3). After Michael-type addition of malononitrile on intermediate **A**, the reaction is followed by attack of hydroxyl group on one of two nitrile groups. Cyclization and subsequently tatumerization affords the target product.

We extended the model reaction using different derivatives of benzaldehyde. It was revealed that the electronic nature of substituted groups on benzealdehyde could intensely affect reaction times and chemical yields. Reaction efficiencies were improved by changing the substituent groups from methoxy to Br and then Cl. Surprisingly, the presence of more strong electron-withdrawing groups, such as NO_2 and CN, altered the results (Table 4). This contradictory behavior could be the consequence of a change in the rate-determining step. It is conceivable that the first step, nucleophilic attack of pyrrole to the aldehyde, might be the rate-determining step, which can be accelerated by electron-withdrawing groups. However, the second step (dehydroxylation step) could probably become rate-determining step as the substituents become more electron-withdrawing. Because the second step proceeds better with electron-releasing group, the presence of CN and NO_2 groups prolongs the reaction time and decreases chemical yield.

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