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ONE-POT SYNTHESIS OF SOME NEW 4-ARYL-2,6-DI(BENZOFURAN-2-YL)PYRIDINES USING A BRØNSTED-ACID IONIC LIQUID

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Abstract: In the present study,one-pot synthesis of some new 4-aryl-2,6-di(benzofuran-2-yl) pyridines from 2-acetylbenzofuran, aromatic aldehydes and ammonium acetate in presence of 3-methyl-1-(4-sulfonic acid)-butylimidazolium hydrogen sulfate [MIM-$(CH_2)_4SO_3H$][HSO_4], a Brønsted-acid ionic liquid as a green and reusable catalyst in solvent-free conditions are described. The products were characterized on the basis of FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectral and microanalytical data.

Keywords:2,4,6-Triarylpyridines, Kröhnke pyridines, Three-component condensation, Aromatic aldehydes, Brønsted-acid ionic liquid.

Introduction

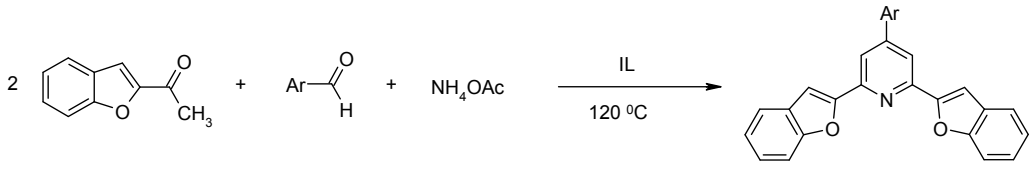
The wide-ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.[i-iv] In addition to these important biological applications, pyridine is also of great utility in preparative organic and coordination chemistry.[v, vi]

In the literature, a number of methods have been reported for the synthesis of 2,4,6-triarylpyridines (Kröhnke-type pyridines).[vii]Previously, 2,4,6-triarylpyridines have been prepared by the condensation of 1,5-diketones with formamide-formic acid[viii] and by other synthetic procedures including the Chichibabinmethod.[ix, x] Following these procedures, the yields of single products are low because of the formation of mixtures of pyridines and various by-products.[x] These compounds have also been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate.[vii, xi] However, the pyridinium salts and the unsaturated ketones have to be synthesized first, so this method is relatively expensive. More recently, the most general synthetic approach for preparation of 2,4,6-triarylpyridines involves one-pot reaction of arylmethyl ketone, aldehyde and ammonium acetate both with and without catalyst. [xii-xiv]

Due to the wide spectrum of activities shown by benzofuran moiety, various substituted benzofurans with various substituents at different positions have been synthesized.[xv, xvi] Also, reactions of benzofuran derivatives were studied and have been applied to the synthesis of more complex valuable materials. 2-Acetylbenzofurans have been employed successfully as starting materials for the production of biologically active compounds. The reaction of $NADP^+$ (an

oxidized form of nicotinamide adenine dinucleotide phosphate) with 2-acetylbenzofuran produced a fluorescent product, allowing the highly-sensitive and quick detection of $NADP^+$. This method was successfully applied to the detection of P450 substrates in the microtiter-plate format.[xvii]

In this paper we wish to report an efficient approach to the synthesis of some new 2,6-di(benzofuran-2-yl)-4-aryl pyridines (**3a-h**), using 3-methyl-1-(4-sulfonic acid)-butylimidazolium hydrogen sulfate [MIM-$(CH_2)_4SO_3H$][HSO_4], a Brønsted-acid ionic liquid (**IL**),[xviii] as a green and reusable catalyst (**Figure 1**).



(1) **(2a-h)** **(3a-h)**

Figure 1: Synthesis of 4-aryl-2,6-di(benzofuran-2-yl)pyridines.

Results and discussion

To determine the most appropriate conditions and evaluate the catalytic efficiency; initially a model study was carried out on the synthesis of 2,6-di-(benzofuran-2-yl)-4-phenyl pyridine (**3e**). Among different solvents (ethanol, methanol, toluene, DMF, THF, DMSO, CH_3CN) screened and solvent-free system, condensation of 2-acetylbenzofuran, benzaldehyde, ammonium acetate and 10% mole ratio of the catalyst is more facile and proceeded to give highest yield, under solvent-free conditions. To evaluate and optimize the catalytic system, the effect of the catalyst to substrate molar ratio on the reaction was investigated in the model reaction (**3e**).It was found that the use of 5% mole ratio of catalyst gave low yield even after longer reaction duration. In comparison, 10% mole ratio of the catalyst led to a 80% yield of product. Increasing in the amount of catalyst could not bring much better results (**Table 1**).

Table 1: Effect of the amount of the catalyst on the reaction.

Catalyst (mol %)	Time (min)	Yield (%)
5	90	52
10	60	80
15	60	81

Therefore, to evaluate the generality of the process, several derivatives of the title compounds with different substituent were synthesized with 10% mole ratio of the catalyst.

The reaction of 2-acetylbenzofuran with various aromatic aldehydes bearing electron-withdrawing groups or electron-releasing groups, and ammonium acetate was carried out under optimized reaction conditions.The electroniceffects and the nature of the substituents on the aromatic ring of aldehydes did not show strongly obvious effects in terms of yieldsunder the present reaction conditions.The results obtained in the current method are illustrated in **Table 2**.

Table 2: Solvent-free synthesis of 4-aryl-2,6-di-(benzofuran-2-yl) pyridines.

product	Ar	Yield (%)	M.p. (°C)	Yield (%)[xvi]	M.p. (°C)[xvi]
3a	4-MeC_6H_4	83	250-252	-	-
3b	4-ClC_6H_4	80	253-254	70	258
3c	4-BrC_6H_4	74	261-263	-	-
3d	4-OHC_6H_4	79	280-282	-	-
3e	C_6H_5	80	214-216	70, (75)[xix]	245, (220-221)[xix]
3f	4-$MeOC_6H_4$	85	211-213	65	253
3g	3-ClC_6H_4	78	197-199	-	-

3h	3-BrC_6H_4	71	212-214	-	-

The resulting products were analyzed by physical and spectral data, melting point, FT-IR, ^1H and ^{13}C NMR, and elemental analyses. For example, the ^1H NMR spectrum of (**3e**) was shown in **Figure 2**, and showed the expected multiplicity and integration values.

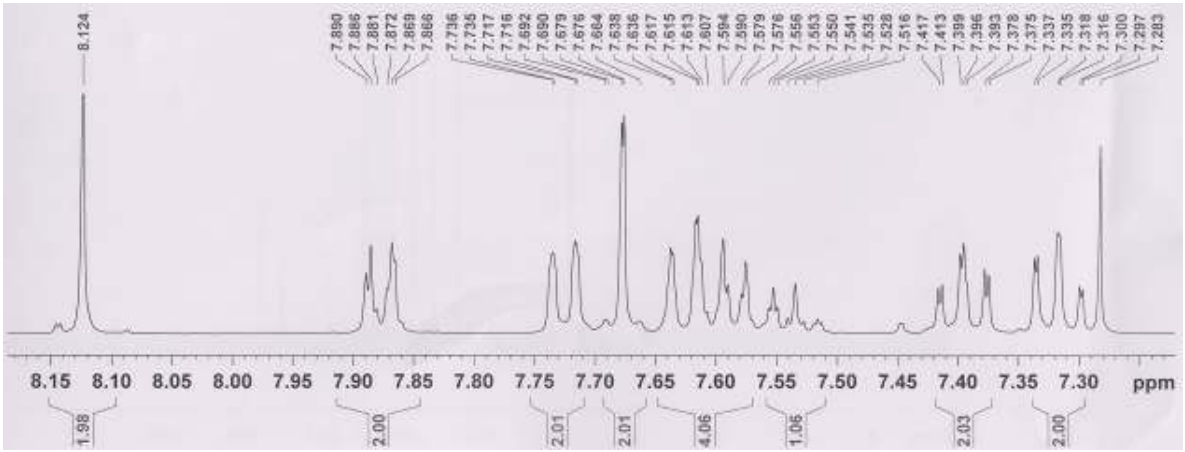


Figure 2: ^1H NMR spectrum of (**3e**)

In conclusion, we have reported a highly efficient and easy access method for the synthesis of 4-aryl-2,6-di-(benzofuran-2-yl)pyridines. Our method has several advantages including mild conditions, good yields, use of inexpensive, recyclable and reusable catalyst, utilize cheap available ammonium source, simple operation and work-up. Additionally, the protocol does not require volatile and hazardous organic solvents. The elimination of the solvent has obvious environmental benefits in regard to the depletion of solvent waste, the simplicity and efficiency of the overall process. Previously, some of 2,6-di-(benzofuran-2-yl)pyridines have been synthesized by nucleophilic substitution of pyryliumteterafluoroborate salt derivatives of benzofuran with NH_4OAc or by cyclisation 1,5-dicarbonyl derivatives of benzofuran with ammonium acetate in solvent condition.[xvi]In this method, the pyryliumsalts and the 1,5-dicarbonyl compounds have to be synthesized first, so this method is relatively expensive.

Experimental

All the chemicals were purchased from Merck and Fluka Company. 2-acetylbenzofuran was prepared according to the literature procedure.[xv] Melting points were obtained in open capillary tubes and were measured on an Electrothermal 9100 apparatus. The IR spectra were recorded on KBr pellets on a Bruker Tensor 27 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 400 DRX Avance instrument. Elemental analysis was performed on a ThermoFinnigan Flash EA microanalyzer. Mass spectra were recorded on Shimadzu GC-MS 17A instrument.

Typical procedure for the synthesis of 4-(Aryl)-2,6-di-(Benzofuran-2-yl)pyridines:

A mixture of an aromatic aldehyde (1.0 mmol), 2-acetylbenzofuran (2.0 mmol, 0.32 gr), NH_4OAc (4 mmol, 0.308 gr) and [MIM-$(CH_2)_4SO_3H$][HSO_4] (10 mol%) was heated on an oil bath at 120 °C. The progress of the reaction was monitored by TLC. After completion of the reaction (60 min.), the reaction mixture was cooled to room temperature, cold ethanol was added to the mixture and the precipitate was filtered off, washed with ethanol, and dried.

Reusability of the catalyst:

The Brønsted-acid ionic liquid catalyst, [MIM-$(CH_2)_4SO_3H$][HSO_4], was soluble in water, therefore it is retrievable from reaction mixture. Then the catalyst was washed with diethyl ether,

dried in vacuum oven at 50 °C for 2 h, and reused in another reaction. The recycled catalyst was used for three further reactions without observation of appreciable lost in its catalytic activities.

Spectral data of 4-aryl-2,6-di-(benzofuran-2-yl)pyridines.

2,6-di(benzofuran-2-yl)-4-p-tolyl pyridine **(3a):** Light yellow crystals; FT-IR (KBr) (υ_{max}/cm^{-1}):1548, 1564 (C=N), 1514, 1450 (C=C), 1108, 1174 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.49 (s, 3H, Me), 7.31 (t,*J*=7.2 Hz, 2H, benzo), 7.37-7.41 (m, 4H, benzo), 7.63 (d, *J*=8 Hz,2H, benzo), 7.67 (d, *J*=1.2 Hz, 2H, furan), 7.72 (d, *J*=8 Hz,2H, ArH), 7.79 (d, *J*=8 Hz,2H,ArH), 8.12(s, 2H, pyridine); ^{13}C NMR (100MHz, $CDCl_3$): δ(ppm) 21.75(CH_3), 105.9, 111.95, 116.92, 122.21, 123.64, 125.65, 127.39, 129.37, 130.31, 135.44, 140.01, 150.19, 150.39, 155.67, 155.8; Anal. Calcd. for $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.80; H, 4.61; N, 3.35%; MS: m/z 401.14 (M^+).

2,6-di(benzofuran-2-yl)-4-(4-chlorophenyl) pyridine **(3b):** Colorless crystals; FT-IR (KBr) (υ_{max}/cm^{-1}):1618, 1574 (C=N), 1546, 1494 (C=C), 1175, 1255 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.31(t,*J*=7.2 Hz, 2H, benzo), 7.39(t, *J*=8.4 Hz,2H, benzo), 7.55 (d, *J*=8.8 Hz,2H, ArH), 7.61(d, *J*=8.8 Hz,2H, benzo), 7.66(d, *J*=0.8 Hz,2H, furan), 7.71 (d, *J*=8 Hz,2H, benzo), 7.79(d, *J*=8.8 Hz,2H, ArH), 8.04(s, 2H, pyridine); ^{13}C NMR (100MHz, $CDCl_3$): δ(ppm) 105.70, 111.52, 116.36, 121.85, 123.29, 125.37, 128.43, 128.86, 129.39, 135.62, 136.45, 148.81, 149.98, 154.99, 155.39; Anal. Calcd. for $C_{27}H_{19}ClNO_2$: C, 76.87; H, 3.82; N, 3.32. Found: C, 76.55; H, 3.61; N, 3.45%; MS: m/z 421.10 (M^+).

2,6-di(benzofuran-2-yl)-4-(4-bromophenyl) pyridine **(3c):** Light yellow crystals; FT-IR (KBr) (υ_{max}/cm^{-1}):1617, 1572(C=N), 1544, 1489(C=C), 1175, 1255 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.31(t, *J*=7.2 Hz,2H, benzo), 7.40(t, *J*=7.2 Hz,2H, benzo), 7.61(d, *J*=8.4 Hz,2H, ArH), 7.66(d, *J*=0.4 Hz,2H, furan), 7.71(m, 6H, benzo and ArH), 8.05(s, 2H, pyridine); ^{13}C NMR (100MHz, $CDCl_3$): δ(ppm)105.72, 111.53, 116.32, 121.85, 123.30, 125.38, 128.71, 128.86, 132.36, 136.93, 148.87, 150.01, 154.97, 155.39; Anal. Calcd. for $C_{27}H_{16}BrNO_2$: C, 69.54; H, 3.46; N, 3.00. Found: C, 69.36; H, 3.63; N, 2.88; MS: m/z 465 (M^+).

2,6-di(benzofuran-2-yl)-4-(4-hydroxyphenyl)pyridine **(3d):**Yellow crystals; FT-IR:υ_{max}(cm^{-1}): 3062 (O-H), 1603, 1584 (C=N), 1519, 1540 (C=C), 1111, 1181 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.95(d, *J*=8 Hz,2H, benzo), 7.22(t, *J*=7.2 Hz,2H, ArH), 7.30(t, *J*=7.2 Hz,2H, ArH), 7.54(d, *J*=8.4 Hz,2H, benzo), 7.55(s, 2H, furan), 7.62(d, *J*=7.2 Hz,2H, benzo), 7.66(d, *J*=8.4 Hz,2H, benzo), 7.97(s, 2H, pyridine), 9.52(b, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)105.36, 111.53, 115.78, 116.38, 121.79, 123.36, 125.35, 128.11, 128.30, 128.77, 149.51, 149.79, 155.19, 159.28; Anal. Calcd. for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.47. Found: C, 80.28; H, 4.13; N, 3.56; MS: m/z 403.11 (M^+).

2,6-di(benzofuran-2-yl)-4-phenylpyridine **(3e):**Cream crystals; FT-IR (KBr) (υ_{max}/cm^{-1}): 1686, 1655 (C=N), 1579, 1552 (C=C), 1181, 1243 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.32(t, *J*=7.2 Hz, 2H, benzo), 7.39(t, *J*=8 Hz, 2H, benzo), 7.51-7.55(m, 1H, ArH), 7.58(d, *J*=7.2 Hz, 2H, benzo), 7.62 (d, *J*=8.8 Hz, 2H, benzo) 7.68(d, *J*=1.2 Hz, 2H, furan), 7.72(d, *J*=8 Hz, 2H, ArH), 7.88(d, *J*=8.8 Hz, 2H, ArH), 8.12(s, 2H, pyridine); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 105.53, 11.54, 116.80, 121.80, 123.24, 125.27, 127.18, 128.92, 129.18, 129.41, 138.06, 149.87, 150.16, 155.19, 155.40; Anal. Calcd. for $C_{27}H_{17}NO_2$: C, 83.70; H, 4.42; N, 3.62. Found: C, 83.76; H, 4.53; N, 3.86; MS: m/z 388 (M^+).

2,6-di(benzofuran-2-yl)-4-(4-methoxyphenyl) pyridine **(3f):**Cream crystals; FT-IR (KBr) (υ_{max}/cm^{-1}): 1580, 1611(C=N), 1550, 1565(C=C), 1181, 1243 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.93(s, 3H, OCH_3), 7.10(d, *J*=8.8 Hz, 2H, ArH), 7.31(t, *J*=7.2 Hz, 2H, benzo), 7.39(t, *J*=8.8 Hz, 2H, benzo), 7.62(d, *J*=8 Hz, 2H, benzo), 7.66(d, *J*=0.8 Hz, 2H, furan), 7.72 (d, *J*=8 Hz, 2H, benzo), 7.83(d, *J*=8.8 Hz, 2H, ArH), 8.08(s, 2H, pyridine); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.45 (OCH_3), 105.41, 111.51, 114.57, 116.17, 121.77, 123.21, 125.20, 128.37, 128.94, 130.23, 149.54, 149.77, 155.30, 155.37, 160.80; Anal. Calcd. for $C_{28}H_{19}NO_3$: C, 80.56; H, 4.59; N, 3.36. Found: C, 80.38; H, 4.63; N, 3.48; MS: m/z 417.19 (M^+).

2,6-di(benzofuran-2-yl)-4-(3-chlorophenyl) pyridine **(3g):**White powder; FT-IR (KBr) (υ_{max}/cm^{-1}): 1618, 1561 (C=N), 1545, 1472 (C=C), 1109, 1173 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.32(t, *J*=7.2 Hz, 2H, benzo), 7.40(t, *J*=8 Hz, 2H, benzo), 7.50-7.52 (m, 2H, ArH), 7.63 (d, *J*=8 Hz, 2H, benzo), 7.68 (s, 2H, furan), 7.73 (d, *J*=8 Hz, 2H, benzo), 7.74-7.76 (m, 1H, ArH), 7.85(s, 1H, ArH), 8.07(s, 2H, pyridine); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 105.77, 11.53, 116.56, 121.85, 123.30, 125.39, 125.71, 127.30, 128.86, 129.39, 130.45, 135.20, 139.95, 148.75, 150. 05, 154.94, 155.43; Anal. Calcd. for $C_{27}H_{19}ClNO_2$: C, 76.87; H, 3.82; N, 3.32. Found: C, 76.93; H, 3.67; N, 3.15; MS: m/z 421.72 (M^+).

2,6-di(benzofuran-2-yl)-4-(3-bromophenyl) pyridine **(3h):** Cream crystals; FT-IR (KBr) (υ_{max}/cm^{-1}): 1618, 1592 (C=N), 1562, 1543 (C=C), 1173, 1254 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.32(t, *J*=7.2 Hz, 2H, benzo), 7.40(t, *J*=7.2 Hz, 2H, benzo), 7.45(t, *J*=8 Hz, 1H, ArH), 7.63 (d, *J*=8.4 Hz, 2H, benzo), 7.64-7.65 (m, 1H, ArH), 7.67 (s, 2H, furan), 7.72 (d, *J*=7.6 Hz, 2H, benzo), 7.78(d, *J*=7.6 Hz, 1H, ArH), 7.99(s, 1H, ArH), 8.04(s, 2H, pyridine); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 105.78, 111.56, 116.54, 121.86, 123.30, 125.41, 125.85, 128.85, 130.17, 130.69, 132.31, 140.21, 148.62, 150.02, 154.93, 155.422; Anal. Calcd. for $C_{27}H_{16}BrNO_2$: C, 69.54; H, 3.46; N, 3.00. Found: C, 69.43; H, 3.28; N, 3.52; MS: m/z 466.32 (M^+).

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