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Regioselective synthesis of 3-arylpyrido[2,3-*b*]pyrazines by reaction of arylglyoxals with 2,3-diaminopyridine

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A series of pyrido[2,3-*b*]pyrazine derivatives were synthesized in good to excellent yields by condensation reactions of arylglyoxals with 2,3-diaminopyridine in dimethylformamide and ethanol at 90 ^{o}C.

1. Introduction

Generally, condensation of 1,2-dicarbonyl compounds with aryl 1,2-diamines affording quinoxalines and pyrido[2,3-*b*]pyrazines is an interesting target in modern organic chemistry.[1-3] These compounds have great synthetic potential due to applications in many aspects of pharmaceutical and medicinal chemistry such as antibiotic,[4] potent inhibitors,[5,6] binding to DNA,[7] antimicrobial,[8-10] receptor antagonists,[11,12] activities. The pyrido[2,3-*b*]pyrazines are highly active fungicidal,[13] which are also used in the treatment of several cancer diseases with natural products such as taxol and vinca alkaloids, like vinblastine and vincristine.[14] The traditional methods for the synthesis of quinoxalines and pyridopyrazines generally require high reaction temperature, strong acidic media, and mostly long reaction time, moisture sencitivity as well as high cost, and toxicity of the reagents, therefore, a practical and more efficient alternative is still of interest for direct synthesis of pyrido[2,3-*b*]pyrazines under mild conditions.

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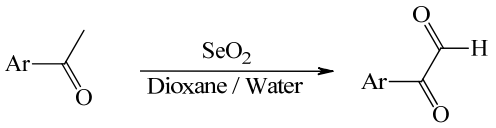
Here, we report an efficient procedure for regioselective synthesis of pyrido[2,3-*b*]pyrazines by one-step double condensation of 2,3-diaminopyridine with a series of arylglyoxals.

2. Results and Discussion

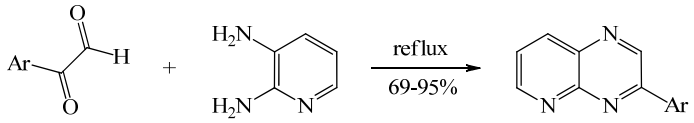
Arylglyoxals (**2a-h**) were prepared by oxidation of related acetophenons by SeO_2, in dioxane and water (Scheme 1).[15]



1 **2**

Scheme 1. Synthesis of Arylglyoxals

Reaction of arylglyoxals (**2a-h**) with 2,3-diaminopyridine (**3**) in dimethylformamide and ethanol at 90 ^{o}C gave the corresponding pyrido[2,3-*b*]pyrazines (**4a-h**) in 69-95% yield (Scheme 2). The products (**4a-h**) are listed in Table 1.

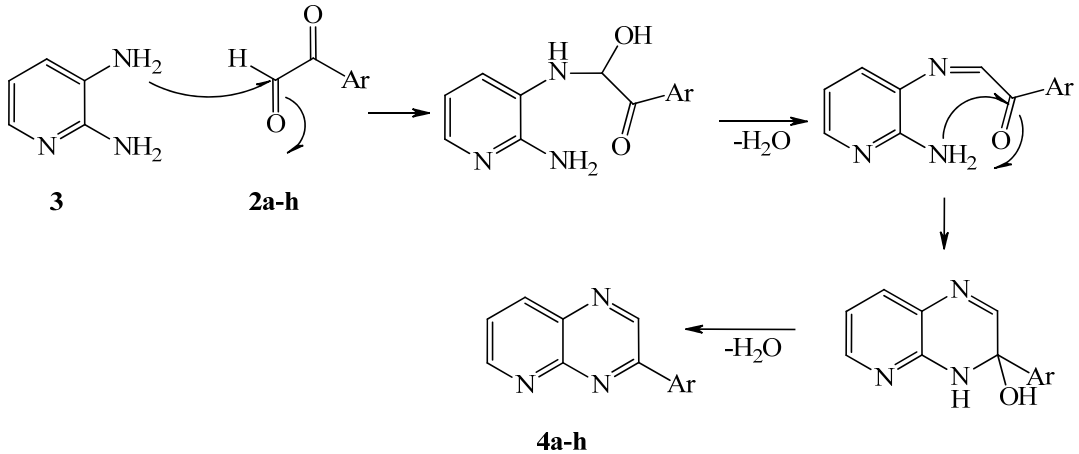


2a-h **3** **4a-h**

a; Ar = C_6H_4 **b**; Ar = 3-BrC_6H_4 **c**; Ar = 4-BrC_6H_4
d; Ar = 3-ClC_6H_4 **e**; Ar = 4-FC_6H_5 **f**; Ar = 4-$NO_2C_6H_4$
g; Ar = 3-$OMeC_6H_4$ **h**; Ar = (3-MeO)(4-OH)C_6H_3

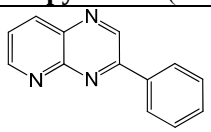
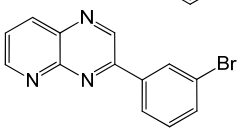
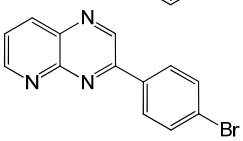
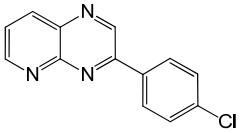
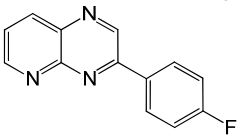
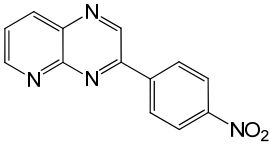
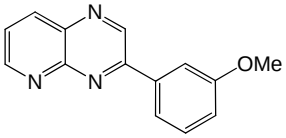
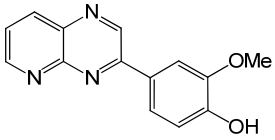
Scheme 2. Synthesis of Pyrido[2,3-*b*]pyrazines (**4a-h**)

It seems that in the first step, the amino group of position 3, which is more active than the amino group in position 2, attacks on the glyoxal′s formyl group. In the second step, condensation amino group in position 2 with keto group and following the loss of two molecules of water will cause the formation of final products (Scheme 3).



Scheme 3. Suggested Mechanism for the Synthesis of Pyrido[2,3-*b*]pyrazines (**4a-h**)

Table 1. List of Pyridopyrazine Derivatives

Entry	Pyridopyrazines (**4a-h**).	Reaction time (hrs)	Yield (%)
4a		8	69
4b		7	78
4c		6.5	93
4d		7	79
4e		6	95
4f		6	81
4g		8	74
4h		7	76

3. Conclusions

The pyrido[2,3-*b*]pyrazine derivatives were obtained by double condensation reaction of 2,3-diaminopyridine with various arylglyoxals in to excellent yields. Simplicity of operation, high yields, short reaction times, good substrate generality are the key advantages of this method. This method of synthesis appear to be generally applicable to the synthesis of pyridopyrazine derivatives which may have pharmaceuitical applications.

Acknowledgements

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Experimental

Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 FT-NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ using TMS as the internal standard. FT-IR spectra were recorded in

KBr disks on Thermo Nicolet (Nexus 670) FT-IR spectrometer. Mass spectra (EI, 70 eV) were recorded on a Varian Matt 311 spectrometer. Elemental analyses were performed on a Leco Analyzer 932. Melting points were determined on a digital melting point apparatus (Electrothermal) and remain uncorrected. Freshly distilled solvents were used throughout, anhydrous solvents were obtained according to Perrin and Armarego.[16]

General procedures for the synthesis of Arylpyrido[2,3-*b*]pyrazines

A mixture of the 2,3-diaminopyridine (1 mmol) and arylglyoxal monohydrate (1 mmol) was heated in dimethylformamide (1 mL) and ethanol (3 mL) for 6-8h, at 90 °C. The progress of reaction was monitored by TLC using CH_3Cl/MeOH (10:1) as eluent. The reaction mixture was cooled to room temperature and the precipitate was filtered and washed with cold ethanol to give the desired product.

3-Phenylpyrido[2,3-*b*]pyrazine (4a)

Brown solid, yield 69%, mp 97 °C. ^{1}H NMR spectrum, δ, ppm: 7.50-7.65 (3H, m, H Ar), 7.74 (1H, dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, H Ar), 8.40-8.34 (2H, m, H Ar), 8.53 (1H, d, J = 8.4 Hz, H Ar), 9.22 (1H, d, J = 4.2 Hz, H Ar), 9.50 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 124.69, 128.31, 129.35, 131.63, 135.18, 136.79, 140.08, 145.08, 149.43, 152.95, 155.41. FT-IR spectrum, ῡ, cm^{-1}: 3052, 1589, 1546, 1442, 1313, 1231, 957, 837, 761, 687, 573. Mass spectrum, *m/z* (I_{rel}, %): 207 $[M]^+$ (3), 152 (15), 104 (10), 103 (50), 77 (62), 76 (69), 75 (52), 52 (97), 50 (100), 39 (55), 38 (52), 28 (70). Found, %: C 75.45; H 4.21; N 20.01. $C_{13}H_9N_3$. Calculated, %: C 75.35; H 4.38; N 20.28.

3-(3-Bromophenyl)pyrido[2,3-*b*]pyrazine(4b)

Brown solid, yield 78%, mp 184 °C. ^{1}H NMR spectrum, δ, ppm: 7.44 (1H, bt, J = 7.8 Hz, H Ar), 7.67 (1H, d, J = 7.8 Hz, H Ar), 7.73 (1H, dd, J_1 = 8.1 Hz, J_2 = 3.9 Hz, H Ar), 8.23 (1H, d, J = 7.2 Hz, H Ar), 8.54-8.48 (2H, m, H Ar), 9.20 (1H, s, H Ar), 9.42 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 116.26, 116.55, 124.81, 130.14, 130.25, 136.70, 138.57, 144.08, 150.42, 153.71, 154.30, 163.15, 166.50. FT-IR spectrum, ῡ, cm^{-1}: 3061, 1564, 1540, 1467, 1419, 1276, 1065, 895, 786, 733, 674, 574. Mass spectrum, *m/z* (I_{rel}, %): 287 $[M+2]^+$ (8), 285 $[M]^+$ (10), 206 (24), 179 (35), 104 (30), 102 (30), 77 (64), 75 (55), 52 (44), 50 (100), 38 (48), 26 (35). Found, %: C 54.42; H 2.99; N 14.55. $C_{13}H_8BrN_3$. Calculated, %: C 54.57; H 2.82; N 14.69.

3-(4-Bromophenyl)pyrido[2,3-*b*]pyrazine (4c)

Brown solid, yield 93%, mp 193 °C. ^{1}H NMR spectrum, δ, ppm: 7.74 (2H, d, J = 8.7 Hz, H Ar), 7.75 (1H, d, J = 7.8 Hz, H Ar), 8.25 (2H, d, J = 8.4 Hz, H Ar), 8.52 (1H, d, J = 8.1 Hz, H Ar), 9.22 (1H, s, H Ar), 9.46 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 124.97, 126.48, 129.61, 132.58, 134.25, 136.98, 139.42, 144.31, 149.80, 153.79, 154.01. FT-IR spectrum, ῡ, cm^{-1}: 3060, 1586, 1588, 1539, 1479, 1397, 1304, 1206, 1119, 1072, 1006, 837, 825, 788. Mass spectrum, *m/z* (I_{rel}, %): 287 $[M+2]^+$ (6), 285 $[M]^+$ (6), 183 (12), 102 (35), 77 (100), 75 (56), 64 (15), 52 (30), 51 (53), 50 (98). Found, %: C 54.33; H 2.91; N 14.71. $C_{13}H_8BrN_3$. Calculated, %: C 54.57; H 2.82; N 14.69.

3-(4-Chlorophenyl)pyrido[2,3-*b*]pyrazine (4d)

Green solid, yield 79%, mp 173 °C. ^{1}H NMR spectrum, δ, ppm: 7.57 (2H, d, J = 8.4 Hz, H Ar), 7.74 (1H, dd, J_1 = 8.1 Hz, J_2 = 3.9 Hz, H Ar), 8.31 (2H, d, J = 8.4 Hz, H Ar), 8.51 (1H, d, J = 7.8 Hz, H Ar), 9.21 (1H, bs, H Ar), 9.45 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 124.95, 129.38, 129.58, 133.89, 136.92, 137.84, 139.08, 144.24, 150.03, 153.78, 154.01. FT-IR spectrum, ῡ, cm^{-1}: 3061, 1593, 1587, 1539, 1479, 1453, 1401, 1304, 1206, 1091, 1009, 837, 788, 557. Mass spectrum, *m/z* (I_{rel}, %): 243 $[M+2]^+$ (3), 241 $[M]^+$ (9), 137 (37), 104 (28), 77 (86), 76 (74), 75 (62), 57 (20), 52 (28), 51 (48), 50 (100). Found, %: C 64.53; H 3.22; N 17.69. $C_{13}H_8ClN_3$. Calculated, %: C 64.61; H 3.34; N 17.39.

3-(4-Fluorophenyl)pyrido[2,3-*b*]pyrazine (4e)
Brown solid, yield 95%, mp 152 ^{o}C. ^{1}H NMR spectrum, δ, ppm: 7.30 (2H, d, *J* = 8.7 Hz, H Ar), 7.74 (1H, dd, J_1 = 8.1 Hz, J_2 = 4.2 Hz, H Ar), 8.38 (2H, bt, *J*= 8.4 Hz, H Ar), 8.52 (1H, d, *J* = 8.4 Hz, H Ar), 9.21 (1H, bs, H Ar), 9.45 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 116.26, 116.47, 124.80, 130.138, 130.25, 136.69, 138.64, 144.10, 150.34, 154.23, 166.50. FT-IR spectrum, ῡ, cm^{-1}: 1601, 1545, 1515, 1484, 1410, 1307, 1273, 1233, 1161, 1118, 840. Mass spectrum, *m/z* (I_{rel}, %): 225 $[M]^+$ (1), 170 (15), 121 (30), 77 (26), 75 (28), 64 (17), 52 (54), 50 (100), 39 (40), 38 (46), 28 (82). Found, %: C 69.48; H 3.32; N 18.77. $C_{13}H_8FN_3$. Calculated, %: C 69.33; H 3.58; N 18.66.

3-(4-Nitrophenyl)pyrido[2,3-*b*]pyrazine(4f)
Brown solid, yield 81%, mp 212 ^{o}C. ^{1}H NMR spectrum, δ, ppm: 7.82 (1H, dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, H Ar), 8.46 (2H, d, *J* = 9 Hz, H Ar), 8.55 (2H, d, *J* = 9 Hz, H Ar), 8.59 (1H, bs, ovetlaped with doublet at δ 8.55, H Ar), 9.28 (1H, bd, *J* = 4.2 Hz, H Ar), 9.55 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 124.35, 125.75, 128.94, 137.65, 138.46, 141.43, 143.95, 149.34, 150.40, 152.18, 155.18. FT-IR spectrum, ῡ, cm^{-1}: 3068, 1603, 1542, 1511, 1483, 1454, 1353, 1324, 1304, 855, 787. Mass spectrum, *m/z* (I_{rel}, %): 252 $[M]^+$ (38), 206 (20), 104 (45), 103 (51), 78 (25), 77 (100), 76 (89), 75 (45), 57 (29), 55 (25), 51 (49), 50 (83). Found, %: C 61.80; H 3.36; N 22.55. $C_{13}H_8N_4O_2$. Calculated, %: C 61.90; H 3.20; N 22.21.

3-(3-Methoxyphenyl)pyrido[2,3-*b*]pyrazine (4g)
Brown solid, yield 74%, mp 104 ^{o}C. ^{1}H NMR spectrum, δ, ppm: 3.97 (3H, s, OCH_3), 7.1 (1H, d, *J* = 8.4 Hz, H Ar), 7.51 (1H, t, *J* = 7.8 Hz, H Ar), 7.75 (1H, dd, J_1 = 8.1 Hz, J_2 = 4.2 Hz, H Ar), 7.88 (1H, d, *J* = 7.8 Hz, H Ar), 7.99 (1H, s, H Ar), 8.53 (1H, d, *J* = 8.1 Hz, H Ar), 9.22 (1H, d, *J* = 4.2 Hz, H Ar), 9.48 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.63, 112.64, 118.11, 120.45, 124.74, 130.19, 136.87, 138.59, 139.30, 144.89, 150.00, 153.60, 154.86, 160.49. FT-IR spectrum, ῡ, cm^{-1}: 3050, 1600, 1565, 1544, 1488, 1466, 1426, 1301, 1242, 1178, 829, 793. Mass spectrum, *m/z* (I_{rel}, %): 237 $[M]^+$ (75), 236 (95), 208 (45), 207 (35), 206 (60), 134 (48), 103 (72), 77 (75), 76 (73), 63 (55), 51 (58), 50 (100), 39 (68), 38 (54). Found, %: C 70.71; H 4.79; N 17.62. $C_{14}H_{11}N_3O$. Calculated, %: C 70.87; H 4.67; N 17.71.

2-Methoxy-4-(pyrido[2,3-*b*]pyrazin-3-yl)phenol (4h)
Green solid, yield 76%, mp 233 ^{o}C. ^{1}H NMR spectrum, δ, ppm: 3.92 (3H, s, OCH_3), 6.98 (1H, d, *J* = 8.4 Hz, H Ar), 7.78 (1H, dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, H Ar), 7.90-7.96 (2H, m, H Ar), 8.50 (1H, d, *J* = 8.4 Hz, H Ar), 9.10 (1H, bs, H Ar), 9.67 (1H, s, H Ar), 9.82 (s, 1H, OH). ^{13}C NMR spectrum, δ, ppm: 56.21, 112.51, 116.39, 122.17, 125.10, 127.15, 136.14, 138.27, 145.09, 148.79, 150.48, 150.69, 154.04, 154.74. FT-IR spectrum, ῡ, cm^{-1}: 3278, 2920, 1594, 1529, 1488, 1401, 1296, 1202, 1171, 1139, 870, 792. Mass spectrum, *m/z* (I_{rel}, %): 253 $[M]^+$ (100), 224 (27), 195 (26), 149 (33), 134 (47), 106 (39), 77 (77), 55 (25), 50 (33). Found, %: C 66.34; H 4.49; N 16.45. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.40; H 4.38; N 16.59.

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