A CONVENIENT CATALYST-FREE SYNTHESIS OF SOME SUBSTITUTED PYRIDINE BENZAMIDES FROM ARYL ALDEHYDES

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A new method of amides synthesis under catalyst-free condition has been developed by using aldehydes and aminopyridines. The amides were synthesized by using different aldehydes and aminopyridines using ethanol as a solvent and hydrogen peroxide as oxidant. The method helps in preparation of amides which were acquired in good yield within 4-5 h using conventional heating. The reaction is catalyst-free. The developed method is easy, economical, and flexible.

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INTRODUCTION

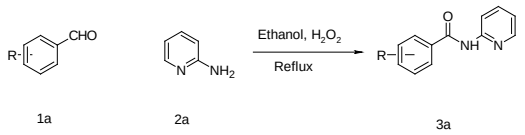
The amide bond is one of the most important functional group. Amides are the precursors of polymers, proteins and many natural compounds.[1] The preparation of peptides involves amide bond formation.[2] The synthesis of amides is generally done by the reaction of amines with active derivatives of carboxylic acid such as anhydrides, acyl halides, aldehydes, and esters.[3] Benzamides having biological significance and potency as effective antihelmintic or antimicrobial agents and proved to be a potent smooth muscle relaxant. Synthesis of these benzamides includes many methods such as the direct conversion of benzene, electrophilic aromatic substitution reaction, etc.[5]

Due to their potential importance in pharmaceutical fields, catalyst-free reactions are the most emerging concept in the last few decades in the organic synthesis.[6,7] A catalyst-free reaction has of extreme significance in decreasing the amount of by-products which avoids purification of compounds.[8] Hydrogen peroxide has high active oxygen content and water as a reduced product which can be easily removed.[9] Ethanol produced from renewable biomass[10] and used as a solvent because of its chemical and toxicological limitation.[11] As it is readily soluble in water thus, it avoids obstruction during workup procedure.[12]

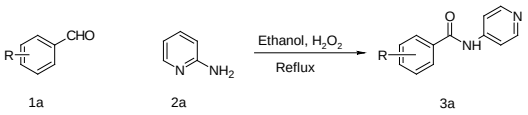
In continuation of our previous work[13-26] for the synthesis of pharmaceutically active materials, an alternative pathway is given for synthesis of pyridine benzamides.

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin-layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. Melting points were recorded on SRS Optimelt. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer, shifts are reported in δ_{ppm} units. The ^{13}C were recorded on a 100 MHz Varian NMR spectrometer.



Scheme 1.



Scheme 2.

General procedure for the synthesis of benzamide compounds

To the mixture of aldehyde (0.1 g, 0.00094 mol) and aminopyridine (1 eq.), ethanol (5-7 mL) was added as a solvent and stirred for 15 min. After the dissolution of reactant, the reaction mixture was refluxed was 4-5 h with the addition of H_2O_2. After the completion of the reaction, the product was extracted with ethyl acetate and water. The solvent was evaporated to dryness to afford the product.

N-(Pyridin-2-yl)benzamide (3a)

^{1}H NMR (400 MHz, DMSO-d_6) 8.41 (d, 1H), 8.15 (d, 1H), 7.99 (d, 2H), 7.80 (t, 1H), 7.49 (d, 2H), 7.15(t, 1H). ^{13}C NMR 165.4, 151.0, 149.2, 137.1, 132.4, 129.3, 129.1, 119.2, 114.8.

4-Chloro-N-(pyridin-2-yl)benzamide (3b)

^{1}H NMR (400 MHz, DMSO-d_6) 8.15(d, 1H), 8.14(d, 1H), 7.95 (d, 2H), 7.80 (t, 1H), 7.55 (t, 1H), 7.48 (t, 2H), 7.17 (t, 1H).^{13}C NMR 165.6, 151.4, 149.2, 138.4, 133.9, 132.4, 128.5, 128.2, 119.2, 114.5.

2-Chloro-N-(pyridin-2-yl)benzamide (3c)

^{1}H NMR (400 MHz, DMSO-d_6) 8.41 (d, 1H), 8.14 (d, 1H), 7.82 (d, 2H), 7.43 (d, 1H), 7.41 (d, 1H), 7.40 (d, 1H), 7.16 (t, 1H). ^{13}C NMR 164.7, 150.8, 149.1, 138.3, 132.2, 131.6, 131.4, 129.9, 129.6, 126.5, 119.2, 115.1.

4-Bromo-N-(pyridin-2-yl)benzamide (3d)

^{1}H NMR (400 MHz, DMSO-d_6) 8.14 (d, 1H), 8.16 (d, 1H), 7.92 (d, 2H), 7.89 (t, 1H), 7.64 (d, 2H), 7.15 (t, 1H). ^{13}C NMR 165.8, 151.0, 149.2, 138.0, 132.7, 131.8, 129.2, 124.3, 119.2, 114.8.

2-Nitro-N-(pyridin-2-yl)benzamide (3e)

^{1}H NMR (400 MHz, DMSO-d_6) 8.41 (d, 1H), 8.26 (d, 1H), 8.03(d, 1H), 7.80 (t, 1H), 7.79 (t, 1H), 7.77 (t, 1H), 7.14 (t, 1H). ^{13}C NMR 164.9, 150.8, 149.2, 147.0, 138.0, 132.4, 131.1, 130.2, 129.5, 124.1, 119.2, 115.1.

4-Methoxy-N-(pyridin-2-yl)benzamide (3f)

^{1}H NMR (400 MHz, DMSO-d_6) 8.41 (d, 1H), 8.15 (d, 1H), 7.87 (d, 2H), 7.81 (t, 1H), 7.15 (t, 1H), 7.02 (d, 2H), 3.81(s, 3H). ^{13}C NMR 165.5, 161.9, 151.0, 149.1, 137.9, 130.1, 128.5, 119.2, 114.8, 113.5, 55.3.

4-Nitro-N-(pyridin-2-yl)benzamide (3g)

^{1}H NMR (400 MHz, DMSO-d_6) 8.40 (d, 1H), 8.33 (d, 2H), 8.12(d, 2H), 7.79 (t, 1H), 7.16 (t, 1H). ^{13}C NMR 166.2, 151.0, 149.4, 149.2, 137.9, 136.3, 128.9, 124.1, 119.2, 114.8.

2,3-Dimethyl-N-(pyridin-2-yl)benzamide (3h)

^{1}H NMR 8.40 (d, 1H), 8.15(d, 1H), 7.80 (t, 1H), 7.65 (d, 1H), 7.15(m, 3H), 2.39 (s, 3H), 2.30 (s, 3H). ^{13}C NMR 165.9, 150.8, 149.1, 138.2, 137.3, 134.4, 134.2, 132.0, 136.2, 125.6, 119.2, 115.1, 20.0, 16.5.

3,4-Dimethoxy-N-(pyridin-2-yl)benzamide (3i)

^{1}H NMR (400 MHz, DMSO-d_6) 8.40 (d, 1H), 8.17(d, 1H), 7.80 (t, 1H), 7.45 (t, 2H), 7.15(t, 1H), 6.98 (d, 3H), 3.87 (s, 3H), 3.91 (s, 3H). ^{13}C NMR 166.0, 152.3, 150.8, 149.2, 149.2, 137.9, 129.2, 122.6, 119.2, 114.6, 111.5, 111.4, 55.9, 55.9.

N-(Pyridin-4-yl)benzamide (5a)

^{1}H NMR (400 MHz, DMSO-d_6) 9.50 (s, 1H), 8.40 (d, 2H), 7.96 (t, 4H), 7.50 (t, 2H), 7.46 (d, 1H). ^{13}C NMR 168.3, 148.9, 143.2, 134.5, 132.4, 128.6, 127.7, 113.7.

2-Chloro-N-(pyridin-4-yl)benzamide (5b)

^{1}H NMR (400 MHz, DMSO-d_6) 9.18(s, 1H), 8.40(d, 2H), 7.99(d, 1H), 7.98(d, 1H), 7.75(t, 1H), 7.47(d, 1H), 7.41(t, 1H), 7.40(d, 1H). ^{13}C NMR 165.1, 148.9, 143.3, 132.2, 131.8, 131.4, 129.9, 126.6, 126.5, 113.4.

2-Nitro-N-(pyridin-4-yl)benzamide (5c)

^{1}H NMR (400 MHz, DMSO-d_6) 9.88 (s, 1H), 8.40 (d, 1H), 8.19 (d, 1H), 8.04 (d, 1H), 7.95 (d, 2H), 7.82 (t, 1H), 7.74(t, 1H). ^{13}C NMR 165.3, 148.9, 147.0, 143.3, 132.4, 131.1, 130.5, 129.7, 123.6, 113.5.

4-Bromo-N-(pyridin-4-yl)benzamide (5d)

^{1}H NMR (400 MHz, DMSO-d_6) 9.88 (s, 1H), 8.40 (d, 2H), 7.93 (d, 2H), 7.86 (d, 2H), 7.65 (d, 2H). ^{13}C NMR 169.6, 149.1, 143.3, 133.7, 131.8, 129.3, 124.3, 113.8.

4-Methoxy-N-(pyridin-4-yl)benzamide (5e)

^{1}H NMR (400 MHz, DMSO-d_6) 8.40 (d, 1H), 7.98 (d, 1H), 7.87 (d, 1H), 7.03 (d, 1H), 3.81 (s, 2H). ^{13}C NMR 169.9, 161.9, 148.9, 143.3, 129.7, 129.1, 113.8, 113.5, 55.3.

RESULTS AND DISCUSSION

The reaction to prepare compound **3a** was screened with different solvents to enhance the competence of the reactants and the results are as summarized in Table 1.

Table 1. Optimization of solvents in the preparation of **3a**

Solvent	Time, h	Yield, %
N,N-Dimethylformamide	29	87
Toluene	12	65
Water	10	75
Ethanol	5	99

It could be observed that other than reported[1] the use of ethanol as a solvent proves beneficial in the percentage yield and reaction time as well. On the reaction with N,N-dimethylformamide, the yield was up to the mark, but the reaction time made us look forward towards other solvents (Table 1). On the other hand, the use of toluene showed a drastic change in the reaction time, but the purification reduced the yield of the compound.

Water gave less percentage yield than expected, but the reaction time reduced to 10 h. Ethanol paved us the way towards a further synthesis because of reduced reaction time and excellent yield.

Table 2. Preparation of 2-substituted pyridine benzamide compounds **(3a-m)** in the presence of H_2O_2 in EtOH

Sr. No	$R^1R^2C_6H_3CHO$	Benzamide product	
		Time, h	Yield, %
3a	R^1=H, R^2=H	4	99
3b	R^1=4-Cl, R^2=H	4	94
3c	R^1=2-Cl, R^2=H	5	95
3d	R^1=4-Br, R^2=H	4	85
3e	R^1=2-NO_2, R^2=H	5	80
3f	R^1=4-MeO, R^2=H	5	95
3g	R^1=4-NO_2, R^2=H	5	90
3h	R^1=R^2=Me	4	87
3i	R^1=R^2=MeO	5	92

In preparation of 4-substituted pyridine benzamide (**5a**) (Scheme 2), the optimization of different solvents (Table 2) gave us similar results as were established in case of 2-substituted pyridine derivative (**3a**). The yield and the time required for the reactions were quite similar to those of compound **3a**.

Table 3. Optimization of solvents in the preparation of **5a.**

Solvent	Time, h	Yield, %
N,N-Dimethylformamide	29	84
Toluene	12	55
Water	10	80
Ethanol	5	95

Table 4. Preparation of 4-substituted pyridine benzamide compounds **(5a-e)** in the presence of H_2O_2 in EtOH

Sr. No	$R^1R^2C_6H_3CHO$	Benzamide product	
		Time, h	Yield, %
5a	R^1=H, R^2=H	5	88
5b	R^1=2-Cl, R^2=H	4	95
5c	R^1=2-NO_2, R^2=H	4	83
5d	R^1=4-Br, R^2=H	5	80
5e	R^1=4-MeO, R^2=H	4	92

CONCLUSION

We have optimized a catalyst-free one-pot synthesis of benzamide from substituted aldehyde and aminopyridines with excellent yields. The solvent as ethanol and oxidant as H_2O_2 plays an important role to give promising yields. As the reaction is catalyst-free, thus this reaction proves to be economical and advantageous.

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