International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 04 | April - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Conventional Method for the Synthesis of series of N-phenyl Nicotinamide Analogous Promoted by Iodine

M.Sai Ganesh[1], L. Nagakiran [1], K.D.Prabodh[1], Dr. N. Krishnarao [1*].

1*.Department of organic chemistry, PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India

ABSTRACT:

In the present study, the conventional process of bioactive synthesis of N-phenyl Nicotinamide analogous. These derivatives (4) can be synthesized from nicotinoylchloride (2) with the different substituted aromatic amines (3) in the presence of I_2/K_2CO_3 ethanol at reflux. The nicotinoylchloride (2) can be prepared by nicotinic acid with thionyl chloride in the presence of MDC at 40^0C. All desired compounds were evaluated by ^{1}H-NMR and ^{13}CNMR spectroscopy and LCMS. These new N-phenyl Nicotinamide derivatives were examination pharmacological activities in microbial activity. Some of tested compounds exhibited strong activity while the other showed moderate against.

KETWORDS:

Nicotinoylchloride, aromatic amines, I_2, N-phenyl Nicotinamide, Antimicrobial activity

1. Introduction:

The amide bond is of particular significant, not only for its key function in peptide structures, but also its role in a major of natural and synthetic molecules and polymers [1, 2]. The formation amide bond is traditionally acquired through the activation of the carboxylic acid partner using a greater-than-stoichiometric quantity of some complex activating agent such as carbodimide + additives (HOBt, HOAt or Oxyma), Phosphonium or guanidinium salts, etc. The generating a large amount of bi products, whereas amide formation is 'just' about the elimination of one molecule of water. Now adays, a round table dedicated to the improvement of green chemistry research ranked "amide formation avoiding poor atom economy reagents" as a top priority [3].This point is even more crucial, as the formation of amides from carboxylic acid and amines is by far the most used reaction in medicinal chemistry [4]. This review intends to highlight more recent progress in catalytic formation of amide bonds from amines, carboxylic acids and esters (Scheme 1) [5–7]. Recently, these catalytic admiration strategies were covered by Sheppard, Wang and Perrin, who focused on green aspects, perspectives and peptide synthesis [8–10]. General preparations of amide bond formation that do not focus on catalytic direct approaches have also appeared [11, 12]. Catalytic redox reactions starting from aldehydes or alcohols are beyond the scope of this review and, consequently, will not be reported herein [12]. C–H catalytic amidation reactions from nitrene precursors, which cannot be considered as direct amidation of amines, have been recently covered in comprehensive reviews and thus will not be addressed here [13]. This review aims to focus on mechanistic and practical aspects and to discuss substrate tolerance and racemization.

Outgoing progressive work the titled analogous, the simple, easy procedure for the preparation .this method different aromatic amines in the presence of strong base was applied.

2. MATERIALS AND METHODS:

2.1. GENERAL:

All chemicals, solvents were procured from Sigma Aldrich. All commercial chemicals were used without further purification before use, reactions were continuously checked by thin layer chromatography (TLC) on silica gel and visualizing with ultraviolet light (256 and 367 nm), or with iodine vapour. The melting points of the titled derivatives

were determined using a Buchi B-540 capillary apparatus. NMR spectra were measured on a Bruker Advance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) respectively in solvents like $CDCl_3$ and chemical shifts were referenced to the solvent residual signals with respect to tetramethylsilanes. The reaction temperature was monitored by ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70eV) model using direct inlet probe technique and m/z were reported in atomic units per elementary charge.

2.3. EXPERIMENTAL:

2.3.1. The general procedure of Nicotinoyl chloride:

Take dry and clean necks RBF. The starting material niconicacid in dissolved in MDC and Thionyl chloride poured drop wise in above solution into RBF at 5-10^{0}C and also arrangement on the magnetic stirrer containing hot plate. The reaction mixture was continued carried out the reaction for 2 hrs. at 40^{0}C .The progress of the reaction monitored by the TLC (EtOAc : n-hexane = 5:5). After completion of the all reactants was consumed, cooled the reaction mixture at RT. The crude neutralized with as saturated solution of sodium bicarbonate and poured in ethyl acetate. The separated the organic layer and washed with water and separated the ethyl acetate layer. An organic layer can be distilled off under vacuums and solid compound was obtained.

Characterization of Nicotinoyl chloride (2):

Yield:94%, White solid, M.p-152-154°C: ^{1}H NMR (400 MHz, $CDCl_3$)δppm:8.452 (s, 1H,Pyridine), 8.314 (d, J=8.8Hz,1H,Pyridine), 7.820 (d, J=7.2Hz, 1H,pyridine), 7.474 (s, 1H, pyridine), ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 148.22, 145.61, 135.20, 132.04, 128.12, LCMS (m/z): 143.85(M+2); Molecular formulae: C_6H_4NO. Elemental Analysis: Calculated: C- 50.91; H- 2.85; N- 9.90; Obtained: C-50.84; H-2.83; N- 9.68.

2.3.2. The general procedure of N-phenylnicotinamide:

Take dry and clean necks 50 mL RBF. The charge the nicoticchloride with methylene dichloride at 5-10^{0}C temperature which is also arranged on the magnetic stirrer and also containing hot plate. The charge a mixture of substituted aromatic amines into RBF at mixture carried out 40^{0}C. Before start the reaction, the strong base such as Iodine and K_2CO_3 added into the reaction mixture and reaction continued in 5hrs at same temperature and checked by TLC (ethyl acetate and n-hexane). After the completion of the reaction, crude poured in cold water and add 10 mL of 10% saturated solution of sodium bi carbonate added into the solution and charge with ethyl acetate. The ethylacetae layer separated and washed with solution of Brain. Finally separated the ethylacetae layer and distilled off. The desired product separated by column chromatography and also recrystallized with ethanol N-phenylnicotinamide **(4a-4e).**

Characterization of Nicotinoyl chloride (4a-4e):

2.3.2.1. N-phenylnicotinamide (4a):

Yield-85%, color brown solid, m.p.: 158–159^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 10.258(s, 1H, -CONH), 8.621 (s, 1H,Pyridine), 8.245(d, J=8.0Hz,1H,Pyridine), 7.913 (d, J=8.4Hz, 1H,pyridine), 7.647-7.523 (m, 2H, Ar-H), 7.456 (s, 2H, pyridine), 7.387-7.245 (m, 2H, Ar-H), ^{13}C NMR (100 MHz, CDCl3) δppm: 166.81, 146.22, 141.65, 134.13, 131.49, 129.87, 128.65, 128.05,126.22, 123.54. LCMS (m/z): 199.68(M+H); Molecular formulae: $C_{12}H_{10}N_2O$. Elemental Analysis: Calculated: C-72.71; H- 5.09; N- 14.13; Obtained: C-72.70; H-5.08; N- 14.21.

2.3.2.2.2. N-(4-methoxyphenyl) nicotinamide (4b):

Yield: 93%, brown solid, m.p-184-186°C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 10.367(s, 1H, -CONH), 8.775 (s, 1H,Pyridine), 8.415 (d, J=7.4Hz,1H,Pyridine), 7.674(t, J=8.7Hz, 1H,pyridine), 7.687-7.357(m, 4H, Ar-H),3.718(s,3H,CH_3);^{13}CNMR(100 MHz, $CDCl_3$) δppm: 167.76,154.08, 144.66, 142.07, 134.78, 131.27 129.16, 128.77,

125.65, 118.76. LCMS (m/z): 228.94(M^+); Molecular formulae: $C_{13}H_{12}N_2O_2$. Elemental Analysis: Calculated: C-68.41.71; H- 5.30; N- 12.27; Obtained: C-68.35; H-35.22; N- 12.27.

2.3.2.3. N-(4-bromophenyl) nicotinamide (4c):

Yield: 88%, Reddish brown solid,M.p-195-197°C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 10.270(s, 1H, -CONH), 8.724(s,1H,Pyridine), 8.452 (d, J=8.0Hz,1H,Pyridine), 8.149(d,J=7.0Hz, Pyridine), 7.636 (t, J=7.0Hz, 2H,pyridine), 7.547-7.298 (m, 4H, Ar-H), ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 168.65,147.74, 144.33, 136.94, 132.94, 129.55, 128.92, 128.41, 127.03, 112.74. LCMS (m/z): 277.68(M+2); Molecular formulae: $C_{12}H_9N_2OBr$. Elemental Analysis: Calculated: C-52.01; H- 3.27; N- 10.11; Obtained: C-51.94; H-3.25; N- 10.19.

2.3.2.4. N-(4-cyanophenyl) nicotinamide (4d):

Yield: 86%, brown solid, M.p-187-189°C; 1H NMR (400 MHz, $CDCl_3$) δppm: 10.358(s, 1H, -CONH), 8.774 (s,1H,Pyridine), 8.456 (d, J=9.8Hz,1H,Pyridine), 8.154 (d,J=7.4Hz,1H, Pyridine), 7.854-7.684 (m, 2H, Ar-H), 7.621(t, J=7.0Hz, 2H,pyridine), 7.513 (d, J=8.6Hz,2H,Ar-H); ^{13}C NMR (100 MHz, CDCl3) δppm: 169.09,148.71, 144.65,141.38, 135.08, 130.65, 128.62, 126.35, 119.04, 108.62; LCMS (m/z): 224.57(M+2); Molecular formulae: $C_{13}H_9N_3O$. Elemental Analysis: Calculated: C-69.95; H- 4.06; N- 18.82; Obtained: C-69.95; H-4.04; N- 18.91.

2.3.2.5. N-(4-nitrophenyl) nicotinamide (5c) :

Yield: 85%, brown solid, M.p-186-188°C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 10.397(s, 1H, -CONH), 8.755 (s,1H,Pyridine), 8.487 (d, J=7.8Hz,1H,Ar-H), 8.141 (d,J=8.8Hz,1H, Pyridine), 8.058-7.887 (m, 2H, Ar-H), 7.547(t, J=7.8Hz, 2H,pyridine); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 169.74,148.33, 146.62,1414.32, 135.65, 130.74, 127.60, 125.03, 120.62;LCMS (m/z): 243.17(M+); Molecular formulae: $C_{12}H_9N_3O_3$. Elemental Analysis: Calculated: C-59.26; H- 3.73; N- 17.28; Obtained: C-59.19; H-3.71; N- 17.36.

3. BIOLOGICAL ACTIVITIES

3.1. **Antibacterial activity:**

Compounds (4a4-e) were examined for their antibacterial activity by using well diffusion technique of Agar medium. This media was used for the study of bacterial strains broth culture. Test samples were dissolved in DMSO, a negative control and Chloramphenicol (10 µg/50 µL) a positive control was taken as a standard drug, purchased from Himedia, Mumbai. The concentration of 50 µg/50 µL per well was used to assay the activity. Sterile micropipette tips were used to load the wells with the right amount of sample, control, and standard. After inoculation plates were incubated at 37 °C for 36 h. After the incubation period, zone of inhibition diameter for each well was measured in mm. The MIC and experiment performed in triplicates the average values are tabulated in Table-I.

3.2. Antifungal Activity:

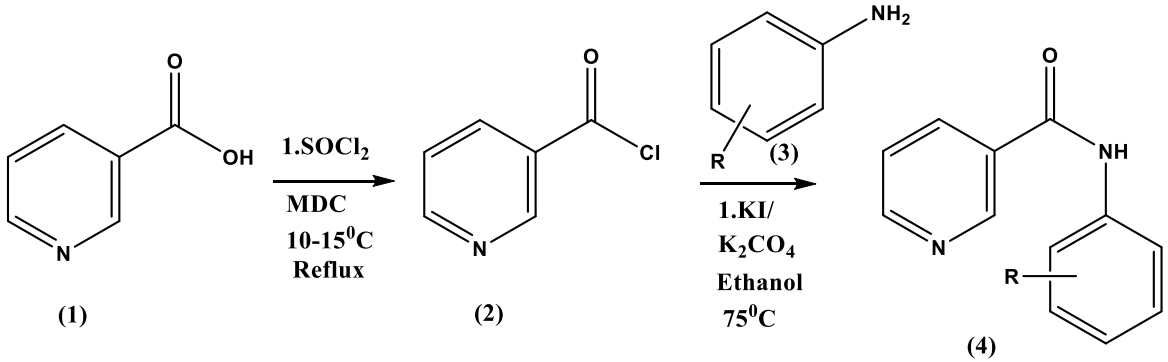
Antifungal activities of all N-phenylnicotinamide derivatives towards two mold fungi were studied, viz. Candida albicans Aspergillus flavus (human pathogen) (mold). The assay the antifungal activity of the synthesized compounds was used poisoned food technique method and Nystatin (10µg/disc) as a standard fungicide. Samples were dissolved in dimethyl sulfoxide (DMSO) a negative control, Nystatin a positive control was taken as a standard drug, purchased from Himedia, Mumbai. The concentration of 50µg/50µL per well was used to assess the activity. Sterile micropipette tips were used to load the wells with the right amount of sample, control, and standard. The plates were then kept at 40^0 C for 24 h to provide sufficient time to diffuse over a considerable area of the plates. After 24h plates were incubated at 25^0 C for 48h. After the incubation period, the Diameter of the zone of inhibition in mm was measured for each well. The MIC and experiment performed in triplicates the average values are tabulated in Table II.

4. RESULTS AND DISCUSSION:

4.1. CHEMISTRY:

Initially, in the present study, conventional method of biological synthesis of N-phenyl Nicotinamide analogous can be done (4). These derivatives (4) can be prepared from nicotinoylchloride (2) with various substituted anilines (3) in the presence of I_2/K_2CO_3 in ethanol at reflux. The nicotinoylchloride (2) can be obtained by nicotinic acid with thionyl chloride in the presence of MDC at reflux.

The results were represented to yields derivatives that the aromatic amines having both electron- releasing and electron-attracting groups were applied and obtained the titled products in good yields. The scope and advantages of the catalyst is having some significant features for the reaction conditions such as the simple work-up procedure, shortest reaction time, an excellent product yields, and purification of products by non-chromatographic methods. It is particularly identified that the different substituted aromatic amines containing electron-donating or electron-donating withdrawing substituents in para-positions lead good yield of the product. Here, we have observed that the reaction of aromatic amines having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups.(Scheme-1):



(Scheme-1)

The structures of the desired compounds were characterized by ^{1}HNMR, ^{13}C NMR, mass spectral and elemental analyses. ^{1}H NMR spectrum showed two singlets at 10.325 which were due to presence of HN-CO amide respectively. Further, an aromatic proton on titled analogous identified that the ring resonated at δ 8.854 and 6.845 and also δ 167.74ppm which confirm the structure. The mass spectrum of 4c exhibited molecular ion peak at m/z : 277.56 (M+2); Molecular formulae: $C_{12}H_9N_2OBr$.

4.2.1. Antibacterial activity:

The *invitro* antibacterial activity of the desired compounds (4a-4e) was compared with standard" Streptomycin'' as collected in (Table-I). As indicated in Table-I, most of the tested derivatives generally showed potent activity against all the tested bacterial strains. The derivatives "4c" exhibited an excellent antibacterial potent activity against gram (+Ve) bacterial strains viz; E.coli, A. and gram (-Ve) bacterial strains viz; Subtilis and S. aureus respectively due to such compounds possesses halogen atoms. The derivatives "4b" exhibited good active potential against bacterial strains. The compounds"4a, 4d and 4e"showed excellent activity against bacterial strains due to compounds are containing highly electron donating groups. These results reveals that the compounds having electron withdrawing groups exhibited good activity than the compounds having electron donating groups. The derivatives containing halogen atoms showed excellent active potential against bacterial strains.

Table-I: Antibacterial activity of the newly synthesized compounds (4a-e):

Zones of inhibition (mm) of compounds (4a–e) against tested bacterial strains:

Compound	Anti-Bacterial Activity			
	Gram(+ ve) bacteria		Gram(- ve) bacteria	
	E. coli	P. aureoginosa	B.subtilis	S. aureus
4a	08	12	10	11
4b	20	21	19	18
4c	24	24	23	22
4d	12	14	12	10
4e	08	09	10	10
Streptomycin	30	30	27	27
DMSO				

Streptomycin was used as standard. a 100 lg/mL of compound in each well.

Values are average of three readings.

4.2.2. Antifungal activity:

The *invitro* antifungal activity of the tested compounds (4a-4e) was compared with standard drug" Ketonozole.'' as collected in (Table-II). The *invitro* antifungal activity of the tested samples (4a-4e) was investigated against A. Niger, A. favas and C.albicans using agar well diffusion assay and zones of inhibition of the test derivatives were expressed in mm as shown in Table-II. Compounds "4c" showed excellent active potential activity against the fungal strain. The compound having "4b" was found to be good active potential against tested fungal strain. Compounds 4a, 4d, and 4e have demonstrated significant antifungal activity comparable to standard. From the results it is reveals that most of the tested derivatives exhibited significant activity and few are moderately active as shown in Table -II. The remaining derivatives exhibited moderate potent activities against Aspergillusfavus. These results reveals that the compounds possess electron donating groups exhibited moderate activity while the compounds having electron attracting groups showed good against the fungal stains.

Table-II: Antifungal activity of the synthesized compounds (4a-e):

Zones of inhibition (mm)a of compounds (4a–e) against tested fungal strains:

Entry	**Anti-Fungal Activity**		
	Aspergillus Niger	**Aspergillusfavus**	**Candida albicans**
4a	07	08	08
4b	14	14	13
4c	18	17	18
4d	11	13	10
4e	09	10	10
Ketonozole	22	22	22
DMSO			

5. CONCLUSIONS

In conclusion, we have reported a direct preparation of conventional process of biological synthesis of N-phenyl nicotinamide derivatives promoted by KI and K_2CO_3. These N-phenyl Nicotinamide analogous can be obtained from nicotinoylchloride with different substituted aromatic amines in the presence of KI and K_2CO_3 in ethanol at reflux. The nicotinoylchloride can be synthesized by nicotinic acid with thionyl chloride in the presence of MDC at reflux. The reaction proceeds at normal temperature in the absence of any metallic catalyst and gives excellent selectivity .In this context, the proposed route gives access to N-phenyl Nicotinamide analogous without salt production and water as by-product.. Therefore, finally, these results gave us insights on the potential intermediates but further studies will be necessary to fully describe the mechanism of this transformation.

6. ACKNOWLEDGEMENTS:

Authors are very thankful to management of PRISM PG&DG College and they were for providing all the necessary facilities.

7. REFERENCES:

1. Greenberg, A.; Breneman, C.M.; Liebman, J.F. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley-Interscience: New York, NY, USA, 2000.

2. Rajput, P.; Sharma, A. Synthesis and biological importance of amide analogues. J. Pharmacol. Med. Chem. 2018, 2, 22.

3. Carey, J.S.; Laffan, D.; Thomsonc, C.; Williams, M.T. Analysis of the reactions used for the preparation of drug candidate molecules. Org. Biomol. Chem. 2006, 4, 2337.

4. Brown, D.G.; Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: Where have all the new reactions gone? J. Med. Chem. 2016, 59, 4443.

5. De Figueiredo, R.M.; Suppo, J.-S.; Campagne, J.-M. Nonclassical routes for amide bond formation. Chem. Rev. 2016, 116, 12029.

6. Ojeda-Porras, A.; Gamba-Sánchez, D. Recent developments in amide synthesis using nonactivated starting materials. J. Org. Chem. 2016, 81, 11548.

7. Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. Catalytic amide formation from non-activated carboxylic acids and amines. Chem. Soc. Rev. 2014, 43, 2714.

8. Sabatini, M.T.; Boulton, L.T.; Sneddon, H.F.; Sheppard, T.D. A green chemistry perspective on catalytic amide bond formation. Nat. Catal. 2019, 2, 10.

9. Wang, X. Challenges and outlook for catalytic direct amidation reactions. Nat. Catal. 2019, 2, 98..

10. Todorovic, M.; Perrin, D.M. Recent developments in catalytic amide bond formation. Pept. Sci. 2020, 112, e24210..

11. Massolo, E.; Pirola, M.; Benaglia, M. Amide bond formation strategies: Latest advances on a dateless transformation. Eur. J. Org. Chem. 2020, 2020, 4641–4645.

12. Santos, A.S.; Silva, A.M.S.; Marques, M.M.B. Sustainable amidation reactions—Recent advances. Eur. J. Org. Chem. 2020, 2020, 2501.