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# An Efficient Synthesis of N-phenylcinnamamide Analogous Employing promoted By $Et_3N$.

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Abstract:

The antibacterial investigation of N-phenylcinnamamide was conducted using the synthetic routes approach (4.With the aid of substituted aromatic anilines (3) and dehydrohalogenating agents such triethyl amine and $Et_3N$ in methylene dichloride at reflux, these derivatives can be produced from cinnamonoyl chloride (2). Cinnamic acid and thionyl chloride can also be combined with MDC at 5-10$^0$C to create compound (2). Elemental analysis can be used to determine the structure of all named compounds and evaluate all derivatives using advanced spectrum data ($^1$HNMR, $^{13}$CNMR, and LCMS). Ant-microbial properties against two fungus strains and four bacterial strains are also evaluated

**KEYWORDS:**

Cinnamoyl glycine, aromatic amines, $Et_3N$, N-phenylcinnamamide, antimicrobial activity

**INTRODUCTION:**

The preparation of amides is one of the most important transformations in organic chemistry and medicinal chemistry and it is one of the rapid frequently performed reactions. In the pharmaceutical industry, the formation of the amide group is pivotal and among the more important transformations in the design of the synthetic drug. New, more an efficient greener stoichiometric methods as well as catalytic strategies have been explained , either for the “classic” coupling approach between an amine and a carboxylic acid and acid derivatives or for more innovative approaches and its mainly involving oxidation procedures to generate amides starting from amines.

The formation of amide bond formation is play an important role and also one of the most frequently used transformations in organic chemistry [1- 4].The most and highly required amide synthesis approached a direct condensation of carboxylic acids and amines. It is satirically hindered by the intrinsic acid–base reactivity of the starting materials. The thermal amide bond formation from the ammonium carboxylate salts requires elevated temperatures [5-7] and it can be used by Lewis acids or boronic acid derivatives. A narrow range of amines and required scavenging the reaction water by large amounts of molecular sieves [8-13] and hence, amides are usually prepared by aminolysis of activated carboxylic acid derivatives, such as halides, anhydrides, azides, or activated esters, that are mostly generated in an extra step with aggressive, expensive or waste-intensive reagents [14-20 ]. The main strategy for amide bond formation involves the in situ reaction of carboxylic acids by peptide coupling reagents, such as carbodimide or Phosphonium salts [21-31] and such amide prepared are highly optimized and provide access to almost any amide structure in near quantitative yields. In modern protein synthesis, they are complemented by efficient chemical and enzymatic peptide ligation methods [32-37].

The path way of the synthesis of titled derivatives from starting material such as cinnamic acid followed by sequential stages followed by Scheme-1.

## 2. Methods and Materials:

2.1. General:

All synthetic grade, chemicals and solvents were commercially procured from Merck chemicals. They were used before without any further purification. All the substituted aromatic amines which were distilled before using the reaction and the following compounds were used as starting materials. The melting points titled compounds were measured Agrawal 520 melting point apparatus and are uncorrected. $^{1}$HNMR and $^{13}$CNMR spectra were recorded on a BRUKER AVANCE 400 MHz and 100MHz using $CDCl_3$ as the solvent.. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer. The development of reactions waschecked by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254aluminum sheets, visualized by UV light.

### 2.2. GENERAL PRODUCER OF CINNAMOYL CHLORIDE:

Take clean and dry 25mL RBF and 25mL methylene dichloride introduced in a RBF and cinnamic acid (10mmol) is dissolved in solvent. The thionyl chloride poured drop wise with help of dropping funnel in a RBF in 5-10$^{0}$C.The total arrangement fitted on the magnetic stirrer. The reaction is continued in 3hrs at reflux. After completion of the reaction time, the mixture cooled under tap water and evaporated the unreacted thionyl chloride and proceeded to the further reaction.

Colourless liquid, Yield-85%,; $^{1}$HNMR (400MHz, $CDCl_3$) ppm: 7.968(s, 1H, CH=CH), 7.554-7.291(m, 5H, Ar-H), 5.547(s, 1H, CH=CH-CO-), $^{13}$CNMR (100MHz, $CDCl_3$) ppm: 190.98, 145.78, 132.65, 128.57, 128.12, 127.99, and 119.02. LCMS (m/z):168.54 (M+2); Molecular formulae: $C_9H_7ClO$; Elemental analysis: Calculated: C- 64.86, H-4.24, Obtained: C- 64.79, H- 4.23.

### 2.2.2.1. SYNTHESIS OF N-PHENYLCINNAMAMIDE (4a-4f):

A reaction mixture of aromatic amines 1 (10 mmol), cinnamoyl chloride (10 mmol), triethyl amines (5 mmol %) in (5 mL) in methylene dichloride was refluxed for 5–10 min and after adding strong base $Et_3N$ as a catalyst. During the reaction, the identified the reaction mixture was monitored by TLC ( 5:5)- Ethyacetate: n-hexane) analysis. After completion of the reaction, the system was cooled to room temperature and the reaction mixtures poured into ethyl acetate and neutralized with a solution of sodium bi carbonate, washed with distilled water (4 mL), and separate the organic layer. The organic layer distilled off under vacuum distillation. All the products were isolated pure just by recrystallization from ethanol, if necessary.

Spectral data for some compounds are as follows:

### 2.2.2.1. N-phenylcinnamamide (5a):

Pale brown solid, Yields – 87%,m.p-174-176; Rf: 0.46 (4:6-EtOAc: n-hexane), IR (KBr cm-1): 3107, 3064, 1788, 1665, 1573, 1542, 1528, 1329, 1234 811; '$^{1}$HNMR (400MHz, $CDCl_3$)ppm:9.120(s,1H,-CONH-),7.612-7.566(m,2H,Ar-H),7.494(s,1H,=CH),7.384-7.287 (m,3H,Ar-H),7.210-7.055(m,2H,Ar-H),7.020(s,1H,=CH),$^{13}$CNMR(100MHz,$CDCl_3$)ppm: 164.45,138.71,130.32,129.86,128.77,128.31,128.29,127.74,125.35,120.07,LCMS(m/z): 228.37 (M-H); Molecular formulae: $C15H_{13}NO$;Elemental analysis: Calculated: C-80.69, H- 5.87, N-6.27; Obtained: C- 8.61, H- 5.86, N- 6.34.

### 2.2.2.2. N-(4-hydroxyphenyl) cinnamamide (5b):

White solid, Yields – 92%, m.p-234-236; Rf: 0.450 (4:6-EtOAc: n-hexane), IR (KBr cm-1): 3106, 3056, 1793, 1657, 1591, 1565, 1551, 1329, 1239, 831 ; $^{1}$HNMR (400MHz, $CDCl_3$)ppm:9.235(s,1H,-CONH-),8.982(s,1H,-OH),7.654-

7.5(m,2H,Ar-H),7.486(s,1H ,=CH),7.412-7.279(m,5H,Ar-H),7.192(s,1H,=CH),6.945-6.835(m,2H,Ar-H);$^{13}$CNMR (100MHz,$CDCl_3$)ppm:164.65,150.43,138.74,132.12,129.86,128.94,128.36,127.88,127.32,125.17,119.21 ;LCMS(m/z): 240.25(M+H).Molecularformule :$C_{15}H_{13}NO_2$. Elemental analysis: Calculated: C- 75.30, H- 5.48, N-5.85; Obtained: C- 75.24, H- 5.47, N- 5.64.

**2.2.2.3. N-(4-methoxyphenyl) cinnamamide (5c):**

White solid, Yields – 94%,M.p-223-225; Rf: 0.45 (4:6-EtOAc: n-hexane IR (KBr cm-1): 3112,3069,1796, 1659, 1589, 1564, 1538, 1266, 832.$^1$HNMR (400MHz, $CDCl_3$)$\delta$ppm: 9. 956(s,1H,-CONH-),7.772(d,J=8.0Hz,2H,Ar-H),7.673(d,J=7.6Hz,2H,Ar-H),7.487 (s,1H,=CH) 7.493-7.288(m,3H,Ar-H),7.095(s,1H,=CH),6.973-6.794(m,2H,Ar-H),3.742(s,3H,-$OCH_3$); $^{13}$CNMR(100MHz,$CDCl_3$)ppm:167.73,155.95,138.76,136.74,129.65,128.79,128.34, 128.05, 124.33,121.56,119.08,54.27.;LCMS(m/z):253.09;Molecularformulae:$C_{16}H_{15}NO_2$;Elemental Analysis: Calculated: C- 75.87 H- 5.97, N- 5.53; Obtained: C- 75.79 , H- 5.51, N- 5.61.

**2.2.2.4. N-(4-chlorophenyl) cinnamamide (5d):**

Pale yellow solid, Yields – 98%, M.p-255-257$^0$C;$R_f$: 0.47 (5:5-EtOAc: n-hexane);IR (KBr cm-1):3091,3054,1785,1649,1591,1564,1546,1325,1234,841;1HNMR(400MHz,$CDCl_3$) ppm:9.134(s,1H,-CONH-),7.845(d,J=7.6Hz,2H,Ar-H),7.567(d,J=8.4Hz,2H,Ar-H),7.488 (s,1H,=CH),7.426(d,J=6.4Hz,2H,Ar-H),7.354(d,J=8.0Hz,2H,Ar-H),7.343(d,J=8.8Hz,2H,Ar-H),7.186(s,1H,=CH);$^{13}$CNMR(100MHz,$CDCl_3$)ppm:167.72,138.58,133.76,131.42,128.58, 128.91,128.73,128.15,127.42,126.38,119.13;LCMS(m/z):259.77(M+H);Molecularformulae:C15H12ClNO;Elemental Analysis: Calculated: C-69.91 , H- 4.69, N- 5.44; Obtained: C- 69.35 , H-4.67, N- 5.51.

**2.2.2.5. N-(4-bromophenyl) cinnamamide (5e):**

Redcompoud, Yields – 88%,M.p-251-253$^0$C ; Rf: 0.46 (5;5-EtOAc: n-hexane), IR (KBr cm-1): 3110, 3087, 1788,1651, 1581,1566, 1544,1341,1240,834; $^1$HNMR (400MHz, $CDCl_3$) ppm:9.254(s,1H,-CONH-),7.873(d,J=8.0Hz,2H,Ar-H),7.751(d,J=6.8Hz,2H,Ar-H),7.495(d, J= 7.2Hz,2H,Ar-H),7.460(s,1H,=CH),7.387(d,J=8.2Hz,2H,Ar-H),7.310(s,1H,=CH),7.274(d,J= 7.6Hz,2H,Ar-H),7.095(s,1H,=CH);$^{13}$CNMR(100MHz,$CDCl_3$)ppm:168.78,141.09,136.72, 131.28,129.54,128.90,128.52,128.25,125.90,122.58,119.24;LCMS(m/z):303.29(M+2); Molecular formulae: $C_{15}H_{12}$BrNO;Elemental analysis: Calculated: C- 59.62, , H- 4.06, N-4.64; Obtained: C- 59.54 , H-4.04, N- 4.72.

**2.2.2.6. N-(4-cyanophenyl) cinnamamide. (5f):**

Yellowcompound,Yields–85%,m.p-245-247$^0$C;Rf:0.45(4:6-EtOAc:n-hexane); ,IR (KBrcm-1): 3109,3065,1794,1658,1575,1554,1538,1322,1237,846; 9.157(s,1H,-CONH-), 7.785(d,J=8.0Hz,2H,Ar-H),7.628(d,J=6.8Hz,2H,Ar-H),7.557(d,J=7.6Hz,2H,Ar-H),7.507 (s,1H,=CH),7.418(d,J=8.0Hz,2H,Ar-H),7.247(d,J=8.0Hz,1H,Ar-H),7.112((s,1H,=CH); $^{13}$CNMR(100MHz,$CDCl_3$)ppm:168.28,141.73,133.09,131.32,129.16,128.81,128.42,127.80,126.33,119.75,118.03,110.84;LCMS(m/z):249.19(M+H);Molecularformulae:$C_{16}H_{12}N_2O$; Elemental analysis: Calculated: C- 77.40, H- 4.87, N- 11.28; Obtained: C- 77.31, H- 4.85, N-11.36.

## 3. BIOLOGICAL ACTIVITY:

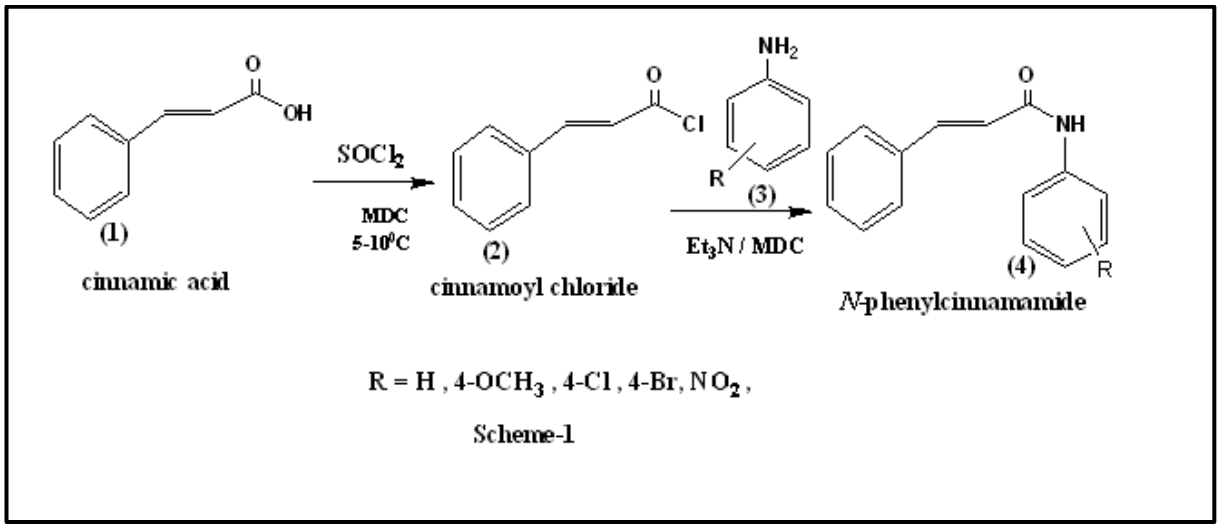
### 3.1. ANTI-BACTERIAL ACTIVITY:

***In vitro*** antibacterial activities of desired synthesized analogous (4a-4f) were evaluated against four human pathogenic bacteria, viz. S. aureas (G–), E .coli (G–), S, typhi (G+) and Bacillus subtilis (G+). The estimation of antibacterial activities is used by the filter paper disc diffusion method. The Streptomycin was used as a standard drug

by the antibacterial activities. The preparation of tested bacterial is a mixture of Nutrient agar (NA) basal medium. The agar media was inoculated with 0.5 ml of 24 h liquid cultures was containing 107 microorganisms/ml and diffusion time was 36 at 25°C for all bacteria and followed by incubation time was 12 h at 37°C. DMSO was used as control Solvent. The diameter inhibition zones were measured by Inhibitory activity of bacterial growth.

plates were incubated at 37.5°C for 48 hrs. Dimethyl sulphoxide (DMSO) was used as solvent to prepare tested solutions (10 mg/ml) of the compounds initially and also to maintain proper **control.**

**4. Results and discussion:**




Scheme-1

By synthesising N-phenylcinnamamide, preliminary research was conducted to ascertain the extent and ideal circumstances for strong bases like triethylamine and solvent MDC. Cinnamoyl chloride, triethyl amines, and substituted aromatic amines were refluxed in methylene dichloride for five to ten minutes. The impact of various catalysts on the synthesis of a series of N-phenylcinnamamide at the right time while taking yield into account. Additionally, we noticed that the electrical characteristics of the substituents on the amines' benzene ring caused the reaction to change in rate. Regardless of whether the amines had an electron-donating or electron-withdrawing substituent, the target molecules (4a–4f) were produced in superior yields.

Although an progressive work on the synthesis of series of N-phenylcinnamamide to be developed by effect strong base to use the various reagents by the several research groups. The fast approach for the synthesis of titled compounds promoted by cinnamoyl chloride and substituted aromatic amines with triethylamine.

During the synthesis of this preparation, we employed carbonyl di imidazole (CDI) as a catalyst and coupling agent. In addition to reducing the by-product, the faster reaction rate increased the yield of the derivatives. Different substituted aromatic amines containing halogen elements and substituents that donate and withdraw electrons. By using a tiny amount of catalyst and acetic anhydride under reflux conditions, it is possible to synthesize N-phenylcinnamamide derivatives in short reaction periods (Scheme-I). In general, 85–92% of named compounds were obtained in the isolated yields. Hydroxyl protons' 1HNMR signals were detected at 8.913 ppm. The-CONH shows 9.102 parts per million. Methoxy proton 1HNMR readings were 3.615 ppm.

The antibacterial activity of desired molecules was screened by bacterial strains .The compounds 4f showed moderate activity against S.auries as well as E.coli. The compounds 4c, 4g, showed good activity against S.typhi as well as B, substills. All rest of the compounds exhibited low to moderate activity. Anti-fungal activity of the target molecules examined against two fungal strains viz, A. Niger as well as C.albicans. The derivatives “4g ” exhibited excellent potent activity as shown table-I.

Table-I. Antimicrobial activity screening activity titled scaffold:

| Compound Code | *Zone of inhibition in (mm) | | | | | |
|---|---|---|---|---|---|---|
| | Bacteria | | | | Fungi | |
| | S.aureus | E.coli | S. typhi | B.substill | A. niger | C. albicans |
| 4a | 08 | 08 | 07 | 06 | 07 | 06 |
| 4b | 12 | 10 | 11 | 13 | 11 | 10 |
| 4c | 17 | 15 | 13 | 16 | 12 | 10 |
| 4d | 19 | 17 | 17 | 18 | 13 | 14 |
| 4e | 17 | 18 | 10 | 14 | 12 | 12 |
| 4f | 21 | 19 | 18 | 19 | 16 | 15 |
| Streptomycin | 25 | 25 | 22 | 22 | NA | NA |
| ketoconazole | NA | NA | NA | NA | 20 | 20 |
| DMSO | --- | ---- | --- | --- | --- | --- |

## 5. CONCLUSIONS:

In conclusion, we have improved an efficient route synthesis of N-phenylcinnamamide derivatives from sequential stages from cinnamic acid via the reaction of strong bas. The catalyst of this process of the synthesis has been advantages commercially available, an easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure. The antibacterial activity of tested moieties was examined by bacterial strains and fungal strains.

## 6. AKOWNLDEMENT:

We would like to acknowledge PRISM PG &DG College, Visakhapatnam for providing us laboratory facility to carry out project work.

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