WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 9, 1800-1809. Research Article ISSN 2277– 7105

AN EFFICIENT IMPROVED SYNTHESIS OF N-PHENYLCINNAMAMIDE ANALOGOUS PROMOTED BY CDI / ET_3N.

D. Ramakrishna, B. Priyanka and Dr. N. Krishna Rao*

Prism Pg & Dg College, (Affiliated By Andhra University), Visakhapatnam, India.

Article Received on
28 March 2023,

Revised on 17 April 2023,
Accepted on 08 May 2023

DOI: 10.20959/wjpr20239-28184

***Corresponding Author**
Dr. N. Krishna Rao
Prism Pg & Dg College, (Affiliated By Andhra University), Visakhapatnam, India.

ABSTRACT

The synthetic pathways protocol followed by antimicrobial study of N-phenylcinnamamide (4).These derivatives can be synthesized from cinnamoylchloride (2) with substituted aromatic anilines (3)in the presence of dehydro halogenating reagent such as triethyl amine and CDI in methylene dichloride at reflux. The compound (2) also can be prepared from cinnamic acid and thionylchloride in the presence of MDC at 5-10^{0}C. All the derivatives evaluated by advanced spectral data (^{1}HNMR, ^{13}CNMR & LCMS) and the structure of the all titled compounds can be determined by elemental analysis. In addition to evaluation of ant-microbial activities against four bacterial strains as well as two fungal strains.

KEYWORDS: Cinnamoylglycine substituted aromatic amines, CDI, N-phenylcinnamamide. Antimicrobial activity.

INTRODUCTION

The synthesis of amides 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 efficient greener stoichiometric methods as well as catalytic strategies have been discussed, either for the "classic" coupling approach between an amine and a carboxylic acid and acid derivatives or for more innovative approaches, mainly involving oxidation procedures to generate amides starting from amines.

Amide bond formation is play important role and also one of the most frequently used transformations in organic chemistry.[1-4] The most required amide synthesis, a direct

condensation of carboxylic acids with amines, is 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], which can be used by Lewis acids or boronic acid derivatives. However, even the best known systems are limited to a narrow range of amines and require scavenging the reaction water, for example, by large amounts of molecular sieves.[8-13] Hence, amides are usually obtained 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 other main strategy for amide bond formation involves the in situ activation of carboxylic acids by peptide coupling reagents, such as carbodimide or Phosphonium salts.[21-31] Such amide syntheses 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 rout way for the synthesis of titled derivatives from starting material such as cinnamic acid followed by sequential steps followed by Scheme-1.

2. METHODS AND MATERIALS

2.1. General

All synthetic grade, chemicals and solvents were procured from SD fine 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 following solvents were applied and were distilled before using. Ethanol (Merck 97%), dichloromethane (Merck, 99%), ethyl acetate (Merck, 98%).The melting points desired compounds were determined on Agarwal 510 melting point apparatus and are uncorrected. 1HNMR and 13CNMR spectra were recorded on a BRUKER AVANCE 400 MHz using $CDCl_3$ as the solvent. FT-IR spectra were recorded on Perkin-Elmer RXI spectrometer. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer. The development of reactions was monitored 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 four necks RBF.25mL methylene dichloride taken in a RBF and cinnamic acid (1mmol) is dissolved in solvent. The thionyl chloride added 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 2hrs 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-89%, IR (KBr cm-1):3149, 3065, 1751, 887; ^{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-4e)

A reaction mixture of substituted aromatic amines 1 (1 mmol), cinnamoyl chloride (1 mmol), triethyl amines (5 mmol %) in (5 mL) in methylene dichloride was refluxed for 5–10 min and after adding 0.1 CDI as a catalyst. During the reaction, the progress of the reaction mixture was checked by TLC (as mobile system 3:7- Ethylacetae: 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 – 86%,m.p-185-186; Rf: 0.432 (4:6-EtOAc: n-hexane), IR (KBr cm-1): 3103, 3065, 1787, 1666, 1579, 1547, 1528, 1325, 1236 814; ^{1}HNMR (400MHz, $CDCl_3$)ppm:9.123(s,1H,-CONH-),7.612-7.523(m,2H,Ar-H),7.492(s,1H,=CH),7.384-7.262 (m,3H,Ar-H),7.210-7.095(m,2H,Ar-H),7.023(s,1H,=CH),^{13}CNMR(100MHz,$CDCl_3$)ppm: 164.97,138.28,130.74,129.15,128.79,128.41,128.28,127.77,125.32,120.02,LCMS(m/z): 22.37 (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 – 91%, m.p-231-233; Rf: 0.450 (4:6-EtOAc: n-hexane), IR (KBr cm-1): 3106, 3056, 1793, 1657, 1591, 1565, 1551, 1329, 1239, 831 ; 1HNMR (400MHz, $CDCl_3$)ppm:9.045(s,1H,-CONH-),8.913(s,1H,-OH),7.612-7.523(m,2H,Ar-H),7.483(s,1H

,=CH),7.402-7.273(m,5H,Ar-H),7.092(s,1H,=CH),6.923-6.735(m,2H,Ar-H);^{13}CNMR (100MHz,$CDCl_3$)ppm:164.15,150.32,138.74,133.12,129.84,128.94,128.36,127.88,127.02,125.19,119.03 ;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 – 92%,m.p-219-221; Rf : 0.450 (4:6-EtOAc: n-hexane IR (KBr cm-1): 3112,3069,1796, 1659, 1589, 1564, 1538, 1266, 832.^{1}HNMR(400MHz,$CDCl_3$)ppm: 9.095(s,1H,-CONH-),7.742(d,J=8.0Hz,2H,Ar-H),7.663(d,J=7.6Hz,2H,Ar-H),7.484 (s,1H,=CH), 7.373-7.276(m,3H,Ar-H),6.912(s,1H,=CH),6.912-6.694(m,2H,Ar-H),3.642(s,3H,-OCH_3); ^{13}CNMR(100MHz,$CDCl_3$)ppm:166.73,154.95,139.76,136.04,129.66,128.89,128.44, 128.15, 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 – 90%, m.p-251-253^{0}C;R_f: 0.450 (4:6-EtOAc: n-hexane);IR (KBr cm-1):3098,3053,1788,1659,1592,1569,1546,1325,1234,841;1HNMR(400MHz,$CDCl_3$) ppm:9.107(s,1H,-CONH-),7.824(d,J=7.4Hz,2H,Ar-H),7.587(d,J=8.4Hz,2H,Ar-H),7.484 (s,1H,=CH),7.423(d,J=6.4Hz,2H,Ar-H),7.355(d,J=8.0Hz,2H,Ar-H),7.322(d,J=8.0Hz,2H,Ar-H),7.086(s,1H,=CH);^{13}CNMR(100MHz,$CDCl_3$)ppm:166.72,139.58,134.76,130.42,129.58, 128.96,128.63,128.35,127.42,126.38,119.13;LCMS(m/z):259.31(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)

Pale red solid, Yields – 90%,248-250^{0}C ; Rf: 0.460 (4:6-EtOAc: n-hexane, IR (KBr cm-1): 3104, 3038, 1789,1656, 1588,1562, 1544,1346,1240,833; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 9.116(s,1H,-CONH-),7.642(d,J=8.4Hz,2H,Ar-H),7.596(d,J=6.4Hz,2H,Ar-H),7.487(d,J=7.6Hz,2H,Ar-H),7.472(s,1H,=CH),7.354(d,J=7.6Hz,2H,Ar-H),7.313(s,1H,=CH);7.286 (d,J=7.2Hz,2H,Ar-H),7.047(s,1H,=CH);^{13}CNMR(100MHz,$CDCl_3$)ppm:166.78,140.09,134.72,132.28,129.08,128.92,128.55,128.29,124.93,122.08,118.22;LCMS(m/z):303.29(M+2); Molecular formulae: C15H12BrNO;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)

Yellowsolid,Yields–87%,m.p-227-229^{0}C;Rf:0.44(4:6-EtOAc:n-hexane); ,IR(KBrcm-1):3108,3062,1793,1657,1574,1553,1539,1321,1238,845; 9.102(s,1H,-CONH-), 7.774(d,J=8.4Hz,2H,Ar-H),7.573(d,J=6.4Hz,2H,Ar-H),7.534(d,J=7.8Hz,2H,Ar-H),7.492 (s,1H,=CH),7.308(d,J=8.4Hz,2H,Ar-H),7.08(d,J=8.8Hz,1H,Ar-H),7.018((s,1H,=CH); ^{13}CNMR(100MHz,$CDCl_3$)ppm:167.28,140.73,134.09,132.32,130.16,128.87,128.46,127.85,126.33,119.75,118.03,110.84;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

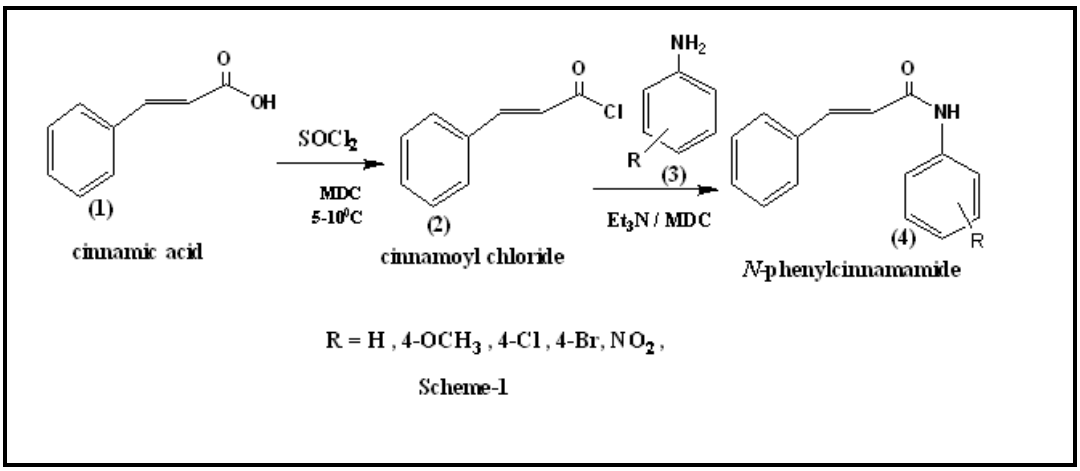
In vitro antibacterial activities of newly synthesized derivatives (4a-f) were examined against four human pathogenic bacteria, viz. S. aureas (G–), E .coli (G–), S, typhi (G+) and Bacillus subtilis (G+). The determination of antibacterial activities is used by the filter paper disc diffusion method. The Streptomycin was used as a standard drug by the antibacterial activities. The preparation of tested bacteria is a mixture of Nutrient agar (NA) basal medium. The agar media was inoculated with 0.5 ml of 24 h liquid cultures containing 107microorganisms/ml and diffusion time was 36 at 25^{o}C for all bacteria and followed by incubation time was 12 h at 37^{o}C. DMSO was used as control Solvent. The diameter inhibition zones were meaured by Inhibitory activity of bacterial growth.

3.2. Anti-Fungal Activity

In vitro antifungal activities of newly desired compounds (4a-f) towards two pathogenic and mould fungi were studied, viz Candida albicans (human pathogen), Aspergillus Niger (mould). The standard drug of fungal activity was used by ketoconazole. Basal medium fortes fungi used to prepare Potato dextrose agar (PDA and also glass petri dishes used were sterilized. Sterilized melted PDA medium (45^{0}C) was poured at the rate of 16 ml into each petridishes (96 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the center of each PDA plate with the help of sterilized needles. Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps. A control disc was also placed on the test plates to compare the effect of the test samples and to nullify the effect of solvent respectively. The plates were then kept in refrigerator at 5^{o}C for 24 h so that the materials had

sufficient time to diffuse over a considerable area of the plates. After this, the 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

Initial investigations involved to determine the scope and optimal conditions for CDI as a catalyst in triethylamine and solvent MDC by synthesis of Synthesis of N-phenylcinnamamide. A reaction mixture of substituted aromatic amines, cinnamoyl chloride, triethyl amines in methylene dichloride was refluxed for 5–10 min and after adding CDI as a catalyst. The influence of various catalysts on employed for the synthesis of series of N-phenylcinnamamide taken as the appropriate time with consideration of yield. Furthermore, we observed that the reaction exhibited to alter the rate of reaction due to the electronic properties of the substituents on the benzene ring of amines. The target molecules (4a–f) were obtained in excellent yields than the regardless of whether the amines containing electron withdrawing or electron-donating substituent.

Although an extensive work on the synthesis of series of N-phenylcinnamamide to be improved by effect catalyst such as CDI coupling reaction reported to use the different reagents as well as catalyst by the several research groups. The fast approach for the synthesis of desired compounds promoted by carbonyl di imidazole cinnamoylchloride and substituted aromatic amines with triethylamine. In this reaction, we used carbonyl di imidazole (CDI) as a catalyst and coupling agent during the synthesis this prepation. The rate of reaction is faster and improved the yield of the derivatives and also reduced the by-product. In a different substituted aromatic amines having both electron-withdrawing and electron-donating substituents and halogen elements. The synthesis of N-phenylcinnamamide derivatives can be

synthesized in short reaction times due utilizing a small quantity of catalyst and also supported by the acetic anhydride under reflux condition (Scheme-I). The isolated yields were generally got 85-92 % of titled compounds. ^{1}HNMR signals of hydroxyl protons showed at 8.913 ppm. The-CONH exhibit 9.102 ppm. ^{1}HNMR values of methoxy protons showed at 3.615ppm.

The antibacterial activity of tilted 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 "5g and 5h" 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	07	06	07	07	06	06
4b	12	10	11	13	11	11
4c	16	17	17	16	12	11
4d	19	17	17	18	13	14
4e	17	18	10	14	12	12
4f	21	20	18	19	13	13
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 CDI. 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 compounds was evaluated 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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