iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 6 **Issue:** V **Month of publication:** May 2018

DOI: http://doi.org/10.22214/ijraset.2018.5074

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 6.887
Volume 6 Issue V, May 2018- Available at www.ijraset.com

Synthesis and Antimicrobial Activity of 2-Amino-4-(2'-n-Butylbenzofurna-3'-YL)-6-ARYL-Nicotinonitriles

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Abstract: 2-amino-4-(2'-n-butylbenzofuran-3'-yl)-6-aryl-nicotinonitriles (4a-4k) have been synthesized. The synthesized products have been assayed for their antimicrobial activity against Gram+ve, Gram-ve bacteria and fungi. All the synthesized products were assigned with IR, [1]HNMR, Mass Spectra, TLC, and elemental analysis. Some of the products showed moderate activity, compare with known standard drugs.

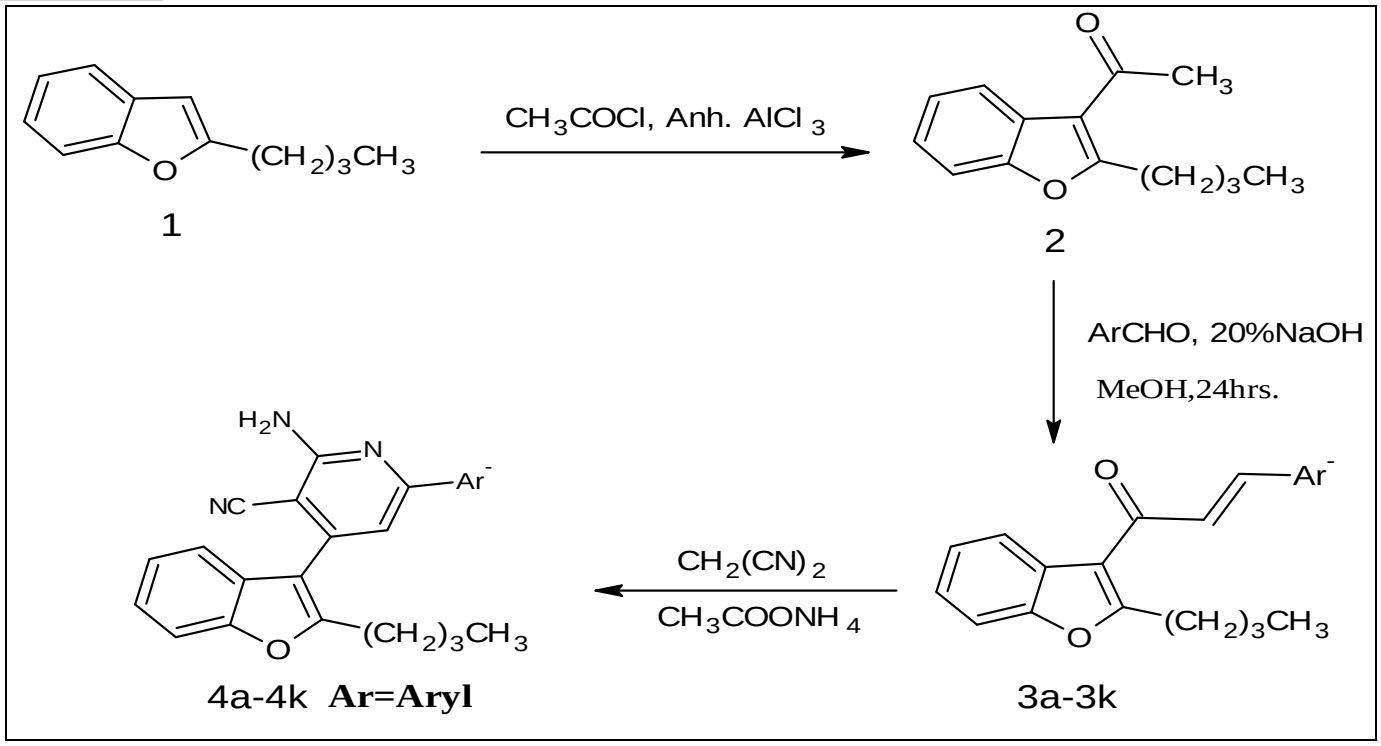
I. INTRODUCTION

Cyanopyridine derivatives showed a vital role largely due to the wide ranging biological activities. Taking into consideration diverse biodynamic activities such as antifungal[1] , Antiepilaptic[2], Antibactrial[3], Anticonvulsant[4], Antitubercular[5], Analgesic[7], Insecticidal[8], Antisoriasis[9], Antihypertensive[10], Anticancer and Anti HIV[11], Antiinfalmmatory[12] etc. In this fact to interesting biological activities, it appeared to interest to synthesized some new cyanopyridine (4a-4k) have been synthesized by the condensation of (E)-1-(2'-n-butylbenzofuran-3'-yl)-3-aryl-prop-2-ene-1-ones with Malononitrile and ammonium acetate. Chalcones of (3a-3k) have been synthesized by the condensation of 1-(2'-n-butylbenzofuran-3'-yl)ethanone with aromatic aldehyde in the presence of aqueous NaOH, 1-(2'-n-butylbenzofuran-3'-yl)ethanone have been synthesized by the acetylation of 2-n-butylbenzofuran with acetyl chloride in the presence of anhydrous $AlCl_3$. All the products (4a-4k) were assigned with IR, [1]HNMR, Mass Spectra, TLC and Elemental analysis. The physical data recorded in Table no: I. Antimicrobial activity recorded in Table no: II and comparable antimicrobial compared with known standard drugs represented in Table no: III.

A. Antimicrobial Activity

All the products (4a-4k) were tested for their antimicrobial activity by Cup-plate method[13] against the Gram positive Bacteria Bacillus megaterium; S.aureus, Gram negative bacteria Escherichia coli, S.Taphimarium and for antifungal activity against Aspergillus niger, Anrobacter awamori at a concentration of 50µg/ml, using DMF as a solvent. After 24hrs of incubation at 37°C, the zone of inhibition were measured in mm. The activity was compared with known standard drugs viz. Ampicillin, Chloramphenicol, Norfloxacin, Fluconazole at the same concentration (50µg/ml) which is represented in Table no II. All the synthesized compounds (4a-4k) showed moderate to good and remarkable activities compared with known standard drugs at same concentration which is represented in Table no III.

II. REACTION SCHEME



A. Experimental Section

All the melting points were measured in open glass capillary method and are uncorrected. IR absorption Spectra (in cm^{-1}) were recorded on a SHIMADZU IR-435 spectrophotometer using KBr pellet method , ^{1}HNMR spectra on BRUKER (300mHz) spectrometer using DMSO as internal standard (chemical shift in δppm) and Mass spectra on a Jeol-JMSD 300 Mass spectrometer at 70ev. The compounds were routinely checked by TLC method using silica gel G.

1) *Synthesis of 1-(2'-n-butylbenzofuran-3'-yl)ethanone :* Methylene dichloride (20ml) was chilled to 0-5°C. Anhydrous Aluminium chloride (2.0gm, 0.015mol) and acetyl chloride (1.0ml, 0.15mol) were added slowly drops by drops at 0-5°C. Reaction mixture was stirred at 0-5°C for 30minutes. 2'-n-butylbenzofuran (1.74gm, 0.01mol)was added slowly to the reaction mass at 0-5°C. After completion of addition, temperature of reaction mass was raised up to 30-35°C. Reaction mixture was stirred at 30-35°C for 4hrs. After completion of the reaction, the reaction mixture was poured in to ice cold water. Layers were separated. Methylene dichloride layer was washed with water. To get required product from Methylene dichloride layer, Methylene dichloride distilled out under reduced pressure. 2-n-butylbenzofuran-3-yl ethanone oily product is formed. Yield: 85.00%, B.P.:87°

2) *Synthesis of (E)-1-(2'-n-butylbenzofuran-3'-yl)-3-(4''-methoxyphenyl)-prop-2-ene-1-one (3e).:* 1-(2'-n-butylbenzofuran-3'-yl)ethanone (2.16gm, 0.01m),4-Methoxybenzaldehyde (1.36gm, 0.01m), methanol(20ml), 20% NaOH (20ml). The reaction mixture was stirred for 24 hrs. at room temperature. Completion of reaction checked with TLC. The reaction mixture was poured into crushed ice, filtered and dried. Yield:78.28% ; M.P.:161°C; (Required: C:79.04;H:6.58%; , $C_{22}H_{22}O_3$; Found: C:79.04 ;H:6.58%;). IR(KBr)(cm^{-1}): 2968(C-H Str. Asym);2832(C-H Str. Sym);1457(C-H Str. Def); 3047(C-H Str., aromatic);1537(C=C-Ring skeletal);1189(C-H Str., i.p.def);728(C-H Str., o.o.P.def); 1680 (C=0 str.); 1138(C-O-C); 1620(-CH=CH Str.);^{1}HNMR (δ ppm0.85-0.89(3H,t,-C<u>H</u>$_3$); 1.22-1.30(2H,m, -C<u>H</u>$_2$-CH$_3$);1.32-1.66(2H,q,-C<u>H</u>$_2$-CH$_2$-CH$_3$);2.51-2.66(2H,t,C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$);3.84(3H,s,-OC<u>H</u>$_3$);6.97-7.86(10H,m,Ar-<u>H</u>).
m/z:334,327,311,301,281,269,246,230,210,209,183,167,144,139,121,108,91,77,64,44,41. Similarly other Chalcones (3a-3k)have been synthesized.

3) *Synthesis of 2-amino-4-(2'-n-butylbenzofuran-3'-yl)-6-(4''-methoxyphenyl)-nicotinonitrile 4e).:* A solution of (E)-1-(2'-n-butylbenzofuran-3'-yl)-3-(4''-methoxyphenyl)-prop-2-en-1-one (3.34gm, 0.01 mol), Methanol (20ml), malononitrile (0.66gm, 0.01mol) and ammonium acetate (1.31gm, 0.01 mol). The reaction mixture refluxed in water bath for 8 hrs. After completion of the reaction, the reaction mixture was poured into crushed ice, filtered and dried. Yield:75.08%; M.P.: 193°C; (Required: C:75.47;H:5.78;N:10.56% , $C_{25}H_{23}O_2N_3$; Found: C:75.45 ;H:5.72;N:10.51%;). IR(KBr)(cm^{-1}): 2968(C-H Str. Asym);2937(C-H

Str. Sym);1459(C-H Str. Def); 3183(C-H Str., aromatic);1511(C=C-Ring skeletal);1176(C-H Str., i.p.def);758(C-H Str., o.o.P.def);1372 (C-N Str.);2117(-C≡N str.); 1243(C-O-C); 1537(C= N Str.); 3341(-N-H Str.); 1632(-N-H bending); ^{1}HNMR (δ ppm): 0.85-0.89(3H,t,-C<u>H</u>$_3$); 1.22-1.28(2H,m, -C<u>H</u>$_2$-CH$_3$);1.30-1.65(2H,q,-C<u>H</u>$_2$-CH$_2$-CH$_3$);2.51-2.64(2H,t,C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$);3.75(3H,s,-OC<u>H</u>$_3$);6.93-7.62(11H,m,Ar-<u>H</u>). m/z:398,209,186,171,157,144(BP),135,121,108,88,80,64,44,41,40 Similarly other Canopyridines (4a-4k) have been synthesized. The physical data of compounds represented in Table-I and antimicrobial activity of compounds (4a-4k) have been represented in Table-II and comparable antimicrobial activity represented in Table-III.

Table- The physical data of compounds (4a-4k)

Compounds	Ar	Molecular formula	M.P. °C	% Yield	%Nitrogen	
					Calculated	Found
4a	C_6H_5-	$C_{24}H_{21}ON_3$	149	79.00	11.43	11.40
4b	2-Cl-C_6H_4-	$C_{24}H_{20}ON_3Cl$	157	77.16	10.45	10.41
4c	4-Cl-C_6H_4-	$C_{24}H_{20}ON_3Cl$	172	80.37	10.45	10.39
4d	4-F-C_6H_4-	$C_{24}H_{20}ON_3F$	180	82.45	10.89	10.75
4e	4-OCH_3- C_6H_4-	$C_{25}H_{23}O_2N_3$	193	75.08	10.56	10.51
4f	2,5-$(OCH_3)_2$- C_6H_3-	$C_{26}H_{25}O_3N_3$	181	83.66	9.82	9.76
4g	3,4-$(OCH_3)_2$- C_6H_3-	$C_{26}H_{25}O_3N_3$	177	78.70	9.82	9.81
4h	3,4,5-$(OCH_3)_3$- C_6H_2-	$C_{27}H_{27}O_4N_3$	215	81.04	9.18	9.15
4i	2-OH-C_6H_4-	$C_{24}H_{21}O_2N_3$	201	83.76	10.95	10.92
4j	3-NO_2-C_6H_4-	$C_{24}H_{20}O_3N_4$	208	87.03	13.57	13.55
4k	4-NO_2-C_6H_4-	$C_{24}H_{20}O_3N_4$	212	90.99	13.57	13.53

Table-II

Compounds	Ar.	Antibacterial activity Zone of inhibition in mm				Antifungal activity Zone of inhibition in mm	
		Gram +ve bacteria		Gram –ve bacteria			
		B.mega	S.aureus	E.coli	S.Taphimarium	A. niger	A. awamori
4a	C_6H_5-	12	14	19	13	12	17
4b	2-Cl-C_6H_4-	13	16	20	17	15	21
4c	4-Cl-C_6H_4-	18	18	22	18	19	16
4d	4-F-C_6H_4-	20	19	18	13	20	15
4e	4-OCH_3- C_6H_4-	12	14	15	15	16	18
4f	2,5-$(OCH_3)_2$- C_6H_3-	13	15	14	12	18	16
4g	3,4-$(OCH_3)_2$- C_6H_3-	14	17	16	17	14	17
4h	3,4,5-$(OCH_3)_3$- C_6H_2-	17	16	18	14	17	20
4i	2-OH-C_6H_4-	13	15	20	18	14	17
4j	3-NO_2-C_6H_4-	15	17	19	16	17	15
4k	4-NO_2-C_6H_4-	18	20	18	19	21	19

Table-III Comparable antimicrobial activity. (Compared with known standard drugs)

Compounds	Maximum antimicrobial activity Zone of inhibition in mm					
	B.mega	S.aureus	E.coli	S.Taphimarium	A. niger	A. awamori
(4a-4k) (50µg/ml)	4d	4d,4k	4a,4b,4c,4i, 4j,4k	4k	4c,4d,4k	4b,4h,4k
Ampicillin 50µg/ml	22	21	20	21	-	-
Chloramphenicol 50µg/ml	21	22	23	20	-	-
Norfloxacin 50µg/ml	23	20	22	21	-	-
Fluconazole 50µg/ml	-	-	-	-	21	21

III. CONCLUSION

The compounds 2-amino-4-(2'-n-butylbenzofuran-3'-yl)-6-aryl-nicotinonitriles (4a-4k) have been synthesized. Some of the compounds **4d,4k** showed good remarkable antibacterial and antifungal activity with compared with known standard drugs e.g: Ampicillin, Chloramphenicol, Norfloxacin and Fluconazole.

IV. ACKNOWLEDGEMENTS

The authors are thankful to principal Smt. S.M. Panchal Science College Talod, (Guj), India and Director, SPC Lifesciences Pvt. Ltd. Baroda (Guj), India for providing research facilities. Thankful to Head, Department of Chemistry, Saurastra University, Rajkot for ^{1}HNMR and Mass Spectral analysis, thankful to Head, Department of Pharmaceutical Chemistry, Saurastra University, Rajkot for IR Spectral analysis and also thankful to, The Director Dr. J.G. Daboriya (Darshan Pharmachem Pvt. Ltd, Ankleshwar) for antimicrobial analysis facilities.

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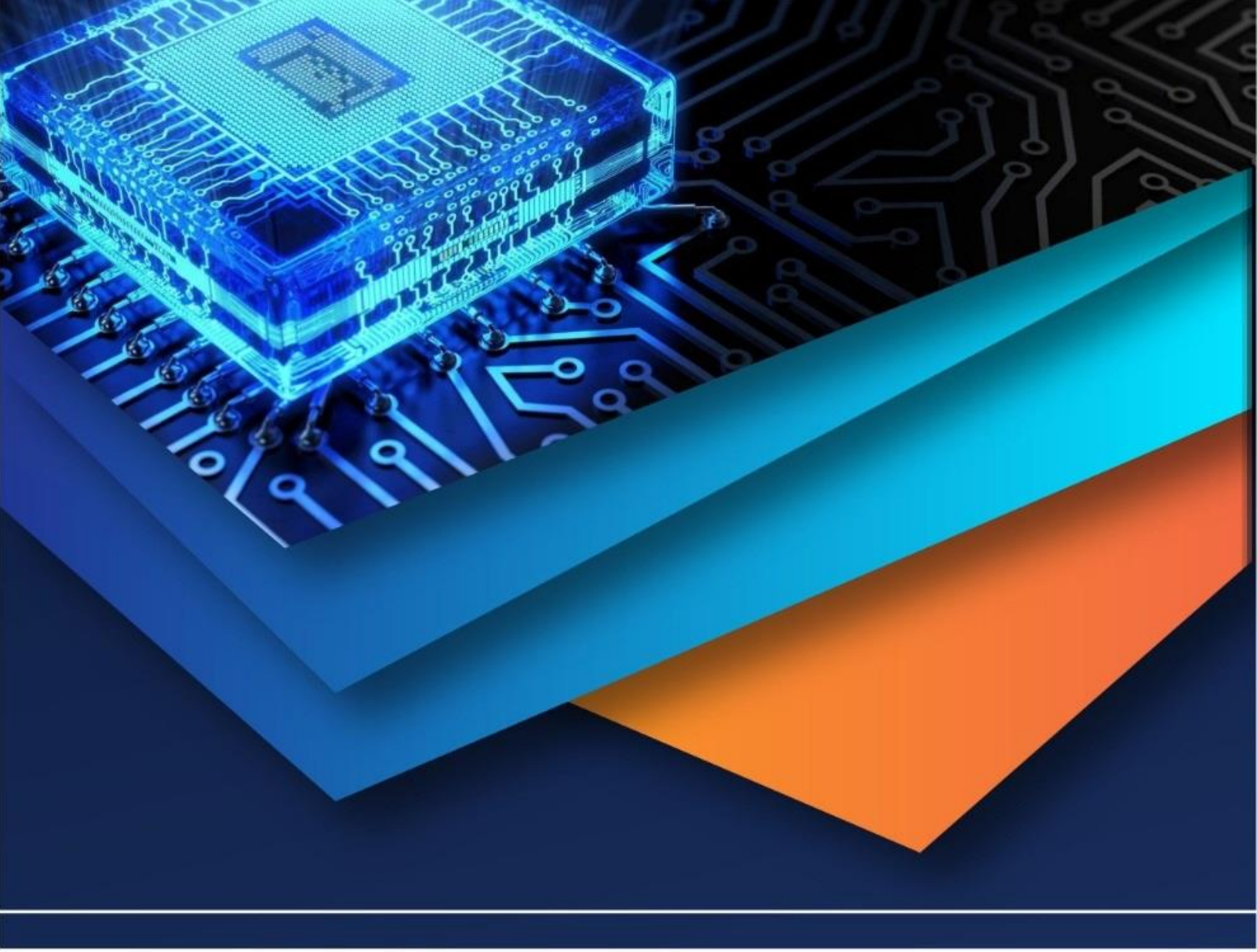

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