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Green Synthesis and Antimicrobial activities of Pyrano[3,2-C]pyridine derivatives

Pushpanjali Sharma[1], Arti Dubey[2], M.K. Dwivedi[3] and Dipak Sharma[4]*

1Department of Biosciences, Acropolis Institute of Management and Research, Indore, 452012 M P, India

2 Department of Chemical Sciences Bhaskar Waman Thakur College of Science Mumbai, Maharashtra, India

3 Department of Pharmaceutical Chemistry Government Holkar Science College Indore, M.P.

4 Department of Chemical Sciences, Maharaja Ranjit Singh College of Professional Sciences, Indore, M P, India

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KEYWORDS

Pyrano[3,2-C]pyridine, Natural catalyst, Antibacterial, antifungal.

ABSTRACT:

Several Pyrano[3,2-C]pyridine derivatives were synthesised using pyridine, malononitrile, aromatic aldehydes and ketones. Using tamarind juice, pine apple juice and apple juice as a natural catalyst along with ethanol as a solvent. Antibacterial and antifungal studies were done on the synthesised derivatives which were found to be active against all the strains used.

1. Introduction

The fused pyrano[3,2-c]pyridine ring skeleton is the most respected heterocycle moiety found in many natural or synthetic products1-3 with a wide range of valuable biological activities, such as antitumor and antituberculosis effects,4-5 Cholinesterase inhibitor6 and antidiabetic7 effects. The biological activities of pyrano[3,2-c]pyridine derivatives are determined by the substituents present in the pyrano[3,2-c]pyridine ring skeleton. More precisely, the synthesis of structurally more varied heterocycles by substituent exchange in a fused pyrano[3,2-c]pyridine ring for bioactive material screening is a viable method to the identification of novel lead compounds. A variety of methodologies exist for the synthesis of pyrano [3,2-c]pyridine derivatives;8-11 As an example, base-catalyzed MCRs of aldehydes, α-methylene carbonyl compounds, and other active methylene compounds can also form a pyrano[3,2-c]pyridine ring.12–14 The pyrano ring is freshly formed between two heterocyclic nuclei, and another heterocycle is either newly formed or partially incorporated into the substrate molecule's chemical structure. For the one-pot reaction, more varied substrates are created and employed in order to attain molecular structural diversity.

2. Objectives

In order to create a variety of pyrano[3,2-c]pyridine derivatives with potential antibacterial properties, we try to supplement a mild and extremely effective one-pot reaction involving aldehydes, ketones, malononitrile, and pyridone in the presence of natural catalysts.

3. Materials and Method:

Materials:

The chemicals required in the synthesis of pyrano[3,2-c]pyridine derivatives were procured from loba. By using an open capillary technique, the melting point was determined. IR spectra were noted on spectrum BX series instrument, 1H NMR spectra were recorded using 400 MHz spectrometer, DMSO-d6 as a solvent and 13C NMR were used to characterize the structures of pyrano(3,2-C)pyridine derivatives. All the above analysis were done at the National Environmental Engineering Research Institute (NEERI) located in Rae Bareli, Lucknow, UP.

Method:

Preparation of Tamarind Juice Ethanolic Extract: The pulp of the tamarind fruit (with seeds and cover) was procured at a nearby market. Five grams of the pulp were soaked in ten milliliters of hot water, and the aqueous

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pulp was then heated in ten milliliters of ethanol for ten to fifteen minutes in a beaker that was covered while the temperature was raised. After filtering the extract, 5 milliliters was utilized as a catalyst.

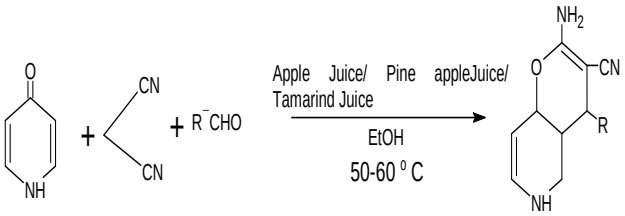
Preparation of Pineapple Juice Ethanolic Extract: Five gram of freshly purchased pineapple was weighed, crushed and then boiled in ten ml of ethanol for ten to fifteen minutes in a beaker that was covered while the temperature was raised. The extract was filtered, 5 ml of which was used as catalyst.

Preparation of Apple Juice Ethanolic Extract: Five gram of freshly purchased apple was weighed, crushed and then boiled in ten ml of ethanol for ten to fifteen minutes in a beaker that was covered while the temperature was raised. The extract was filtered, 5 ml of which was used as catalyst.

Procedure for the Preparation of Pyrano-pyridine derivatives: The Knoevenagel condensation takes place when an active hydrogen molecule and a carbonyl group encounter a nucleophilic addition reaction, which is followed by a dehydration reaction. A prevalent outcome of this reaction is the production of an α,β-unsaturated ketone.

In the present research, equimolar concentrations (0.01m) of malononitrile (2), pyridone (1), and different types of (aromatic/aliphatic) aldehyde/ketone (3) were taken in a round bottom flask and added to ethanol (10 - 15 ml). Using 5ml of tamarind juice/ pineapple juice / apple juice respectively as a catalyst, the reaction mixture was then refluxed for three hours at 50–60°C on the thermostat magnetic stirrer. It was observed that the reaction mixture was heated for only 10-15 minutes, and then it was stirred continuously for three hours. The obtained products (4) were isolated using ice cold water. It was recrystallized from ethanol and dried at room temperature. Thin layer chromatography (TLC) was used to evaluate and verify the purity of the compound, using silica gel G as an adsorbent and an iodine chamber to develop chromatogram.

Reaction Mechanism:



Pyridone (1) **Malononitrile (2)** **(Aromatic/Aliphatic) aldehyde/Ketone (3)** **Product (4)**

Scheme 1: Reaction Catalysed by Tamarind juice/ Apple juice/ Pineapple juice

Table-1: Summary of Reactants, MP and effect on yield by using different catalysts

Reactant (R)	Melting Point / ^{0}C	Yield (%) of different catalysts used		
		Tamarind Juice	Pine apple Juice	Apple Juice
Acetone	152.5	80-90	82	70-80
Anisaldehyde	98.5	85-95	87	80-85
Benzaldehyde	82.5	80-85	83	75-80
Paraformaldehyde	162	80-82	80	80
Benzophenone	62.5	80-85	83	82
Acetaldehyde	119	20-25 (very less)	21(very less)	20- (very less)
Glutaraldehyde	203	25-30 (very less)	25(very less)	25 (very less)
4-nitrobenzaldehyde	113	80-82	81	80
p-dimethylamino benzaldehyde	70	85- 90	85	80-85
Cyclohexanone	60	80-85	82	80-82
Hydroxiqoinone	230	25-30 (very less)	25 (very less)	25 (very less)
Acetophenone	80	35-40	35	35

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Table-2: Aldehyde / Ketone used and products synthesized.

S.No.	1	2	3 (Aldehyde / Ketone)	4 (Products)
1	Pyridone	Malononitrile	Acetone	4a
2			Anisaldehyde	4b
3			Benzaldehyde	4c
4			Paraformaldehyde	4d
5			Benzophenone	4e
6			Acetaldehyde	4f
7			Glutaraldehyde	4g
8			4-nitrobenzaldehyde	4h
9			P-dimethylamino benzaldehyde	4i
10			Cycloxehanone	4j
11			Hydroxiquinone	4k
12			Acetophenone	4l

Antimicrobial Studies

Antimicrobial (antibacterial and antifungal) studies were performed using disk diffusion method or cup plate method. In this method solutions were prepared in DMSO as it was inactive against all the microorganisms and two different concentration (5 µg/ml and 10 µg/ml) of each sample was tested and results were recorded in the form of zone of inhibition. It was observed that nearly all the compounds showed the positive results and were potent antimicrobial.

Antibacterial

The potency of synthesised compounds was tested against Gram-positive and Gram-negative bacterial strain. For antibacterial activity two Gram-negative bacteria Escherichia Coli, Pseudomonal putida and two Gram-positive bacteria Staphylococcus aureus and Bacillus subtilis were used.

Antifungal

For antifungal activity two fungal strains Candida albicans and Aspergillus Sp. were used for determining the antifungal activity of substituted pyranopyridine drivatives.

4. Results

One pot multi component reaction (Knoevenagel mechanism) is a very useful technique to synthesize high yield effective products. Change in reactant causes change in the product. Through thin layer chromatography, the reaction's completion was verified, and the product was separated in ice-cold water. The following compounds were synthesized (4a–l) using the above reaction mechanism. The synthesized derivatives were characterized by IR, 1H-NMR and 13C-NMR and reference spectroscopic range of the same is mentioned in Table-3.

2-Amino-4-(propan-2-ylidene)-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4a) : Yellow colour. IR (KBr) υ, cm-1: 3404-3295 (NH2), 2174 (CN), 1605 (C=C). 13C NMR: 118 (CN), 167 (C), 163(C), 37-45 (CHNH). 1H NMR (400 MHz, DMSO): 0.9 (R-CH3), 1.3 (R-CH2), 4.093 (NH2), 6.9 (aromatic ring), 8-9 (pyridine proton)15.

2-Amino-4-(4-Methoxyphenyl)-4a,5,6,8a-Tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4b) : Off white colour. IR (KBr) υ, cm-1: 3404-3295 (NH2), 2184 (CN), 1607 (C=C). 13C-NMR: 124 (CN), 164 (Ring peak), 39-40 (O-CH3). 1H-NMR (400 MHz, DMSO): 7.2 (pyridine proton), 8.4 (O-CH3)15.

2-amino-4-phenyl-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4c): Light brown colour. IR (KBr) υ, cm-1: 3404-3295 (NH2), 2182 (CN), 1607 (C=C). 13C-NMR : 129 (CN), 24 (R-CH3), 135 (aromatic ring). 1H NMR (400 MHz, DMSO): 7.4 (aromatic ring proton), 6.3 (NH2)15.

2-amino-4a,5,6,8a-hydrohydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4d): Brown colour. IR (KBr) υ, cm-1: 3404-3295 (NH2), 2183 (CN), 1611 (C=C). 1H NMR (400 MHz, DMSO): 4.1 (NH2), 7.3 (aromatic H), 3.4 (aromatic NH)15.

2-Amino-4-(diphenylmethylidene)-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3carbonitrile (4e) : White colour. IR (KBr) υ, cm-1: 3404 -3295 (NH2), 2181 (CN), 1604 (C=C). 13C-NMR: 129 (CN), 137 (aromatic ring), 114 (phenyl ring), 40.3 (pyridine nucleus). 1H-

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NMR (400 MHz, DMSO): 7.7-7.4 (aromatic ring peak)15.

2-Amino-4-methyl-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4f) : Grey colour. IR (KBr) υ, cm-1: 3404- 3295 (NH2), 2181 (CN), 1604 (C=C), 1450 (CH3). 1H NMR (400 MHz, DMSO): δ 3.13 (NH2), 6.39 (aromatic ring). 13C NMR: δ 129 (CN), 140 (aromatic ring)15.

2-Amino-4-(4-oxopropyl)-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4g) : Chocolate brown colour. IR (KBr) υ, cm-1: 3414-3261 (NH2), 2181 (CN), 1604 (C=C), 2830-2695 (aldehyde). 1H-NMR (400 MHz, DMSO): 7.7-7.4 (aromatic ring peak)15.

2-amino-4-nitobenzyl-4A,5,6,8A-tetrahydro-4H-pyrano[3,2-C]pyridine-3-carbonitrile (4h) : Yellow colour. IR (KBr) υ cm-1: 3214 (NH2), 2399 (C-O), 2353 (CN), 1356 (NO2). 1H-NMR (400 MHz, DMSO): δ 7.7-7.4 (aromatic ring peak), δ 3.3 (NH2)15.

2-Amino-4-p-Dimethylaminopropyl-4a,5,6,8a-Tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4i) : Orange colour. IR (KBr) υ, cm-1: 2324 (CN), 1601 (C=C), 812 (ring). 1H-NMR (400 MHz, DMSO): δ 6-7 (aromatic ring peak), δ 0.8 (methyl group peak)15.

2-Amino-4-cyclohexyl-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4j) : Brown colour. IR (KBr) υ, cm-1: 3410-3314 (NH2), 2334-2202 (CN), 1606 (C=C), 3201(O-C), 790 (aromatic ring). 13C-NMR: δ 128(CN peak), δ 112 (aromatic ring)15.

2-Amino-4-(4-hydroxyphenyl)-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4k) : Sticky brown colour. IR (KBr) υ, cm-1: 2213 (CN), 1605 (C=C), 1384 (OH), 1258 (O-C), 1313 (O-H), 826 (aromatic). 1H NMR (400 MHz, DMSO): δ 6.8-6.7 (aromatic ring peak), δ 2.4(methyl grp peak)15.

2-Amino-4-(1-phenylethyl)-4a,5,6,8a-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4l) : Yellow colour. IR (KBr) υ, cm-1: 3415 (NH2), 2205 (CN), 1648 (C=C), 1385 (O-C), 793 (aromatic ring). 13C-NMR : δ 125 (CN peak), δ 119 (aromatic ring)15.

The spectral values obtained were found to be in good agreement to those reported in Silverstien book15.

Table 3: Reference range of Spectroscopy

Spectroscopic Technique	Functional group	Range
IR	Amine	3500-3150 cm^{-1}
	Aromatic ring	3100 – 3000 cm^{-1} 1625 – 1440 cm^{-1} 900-680 cm^{-1}
	C=C	1600-1680 cm^{-1}
	NO_2	1300- 1390 cm^{-1} and 1490-1570 cm^{-1}
	CN	2100-2300 cm^{-1}
	O-C	1000-1500 cm^{-1}
	Alcohols, Esters, Carboxylic Acids, and Anhydrides also absorb in the fingerprint region due to the C-O stretch	1300 – 1000 cm-1
^{13}C-NMR	Aromatic	δ 100-170 and δ 30-50
	CN	δ 120-140
	NO_2	δ 40-70
	Aldehyde and Ketone	δ 170-250
^{1}H-NMR	NH_2	δ 1-3.5
	Aromatics	δ 6-8
	Amide	δ 5.5-8.5
	Methyl	δ 0-2
	Phenols	δ 3.5-5
	CN-CH	δ 1.8-3

Discussion

We can plainly observe From fig. 1, that the percentage yield of product employing the various types of natural catalysts is enough. When compared to all three catalysts, we can observe that utilizing tamarind juice as a catalyst results in a higher production of synthesised derivatives, followed by pine apple juice, which provided a decent yield, and products yielded by apple juice were relatively low.

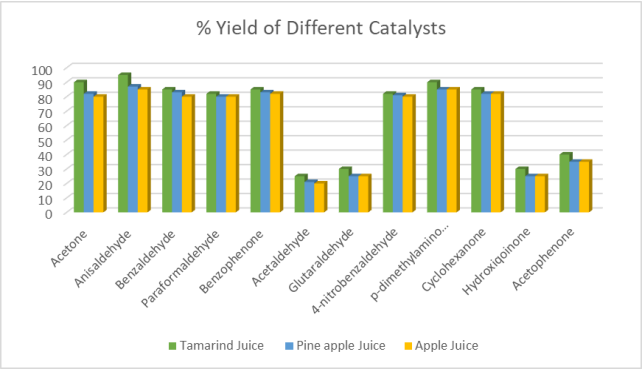

Figure 1: Graphical Representation of Percent Yield of Different Catalysts Used.

Antimicrobial Activities

All the synthesised derivatives have potency against microbes. Pattern of all the graphs shows that increase in

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concentration increases the efficacy of the synthesised derivatives. From the following fig. 2, it can be concluded that all the compounds were active against gram positive bacteria. Derivative 4a is active against both the species of gram positive bacteria but its activity is highest against Streptococcus. 4d and 4e are active against Bascillus while 4j and 4f show good activity against Streptococcus. We can conclude from fig. 3 that 4e is potent antifungal agent for both the species of fungus in all the concentration. 4h and 4j are also good antifungal agent in higher concentration against C. albicans and A. niger. Fig. 4 represents the activity of synthesised compounds against gram negative bacteria. From the graph we can summarize that all the compounds show antimicrobial activity. Amongst all 4a and 4b have highest efficacy against Pseudomonas species and E.Coli.

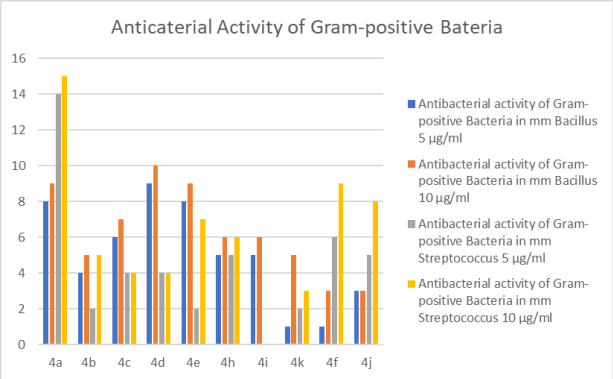

Figure 2: Graphical representation of Antibacterial activity of gram positive Bacteria.

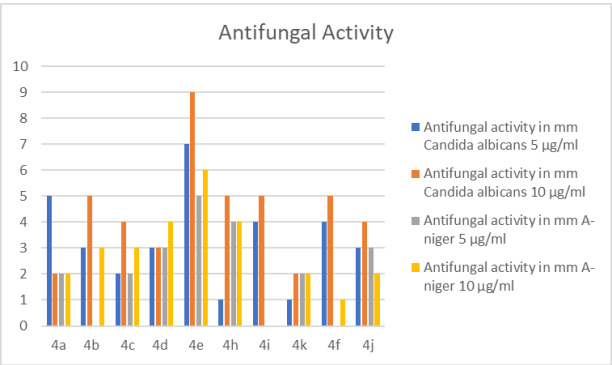

Figure 3: Graphical representation of Antifungal activity of pyranopyridine derivatives.

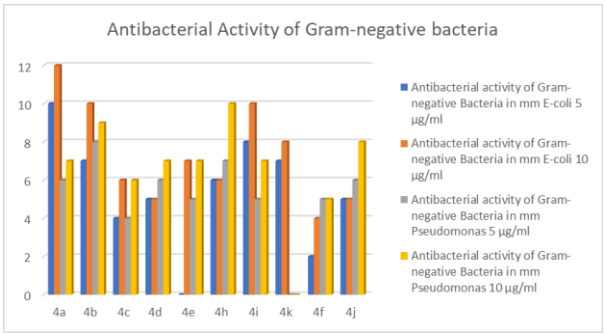

Figure 4: Graphical representation of Antibacterial activity of gram negative Bacteria.

5. Conclusion

When compared to all three catalysts, we can observe that utilizing tamarind juice as a catalyst results in a higher production of synthesised derivatives, followed by pine apple juice and apple juice as shown in fig 1. It was also observed that aliphatic ketones and aromatic aldehydes were highly reactive during the reaction, and the product yield was also better than that of aromatic ketones and aliphatic aldehydes. While studying antimicrobial activities it was observed that all the synthesised derivatives were found to be active against all the species, increase in concentration also enhanced the activity against the microbes. Of all synthesized derivatives 4a is active against both the species of gram positive bacteria but its activity is highest against Streptococcus. 4d and 4e are active against Bascillus while 4j and 4f show good activity against Streptococcus. 4h and 4j are also good antifungal agent in higher concentration against C. albicans and A. niger. 4a and 4b have highest efficacy against Pseudomonas species and E.Coli.

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