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Utilization of Multi Component Reactions in the Synthesis of 1,6-Naphthyridine Derivatives with Expected Biological Activity

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Abstract

We have achieved the diastereo selective synthesis of pyrano and furano naphthyridine derivatives through the utilization of Camphor sulfonic acid (CSA) as a catalyst in an ABB' type multi component coupling reaction involving 4-aminopyridine and cyclic enol ethers to form of pyrano and furano naphthyridine in high yields, primarily exhibiting cis diastereo selectivity. Notably, the addition of water as a reagent causes a shift in diastereoselectivity towards the trans isomer. Synthesized compounds were evaluated in vitro for their antimicrobial activities and molecular docking studies were performed.

Keywords: Pyrano naphthyridine, Furano naphthyridine, Camphor sulfonic acid, Cycloaddition, Organo catalyst.

1. Introduction

The naphthyridine moieties are naturally widespread and exhibit a diverse range of biological activities. Pyranoquinolines are present in various alkaloids such as veprisine, flindersine, and orisine, while furanoquinolines are found in alkaloids [1] like skimmianine [2] and floxuridine [3]. These alkaloids display significant biological properties, including psychotropic effects [4], antiallergic [5], anti-inflammatory [6], and estrogenic activities [7]. Several synthetic methods have been developed for their synthesis. Among these, the [4+2] cycloaddition reaction between *N*-arylimines and electron-rich dienophiles stands out as a potent route for constructing *N*-containing six-membered heterocyclic compounds [8]. Various novel synthetic methodologies have been reported for the synthesis of pyrano and furanoquinoline derivatives. Pyrano naphthyridine derivatives have been synthesized through aza-Diels-Alder reactions catalyzed by Lewis acids [9], metal triflates, and protonic acids [10] such as HCl and trifluoroacetic acid. The aza-Diels-Alder reaction catalyzed by Lewis acids [11], is the preferred method for the synthesis of pyrano/furanoquinoline derivatives. However, many Lewis acids are prone to deactivation or decomposition when exposed to nitrogen-containing reactants, necessitating the use of larger stoichiometric amounts of Lewis acid. Heterogeneous catalysts like montmorillonite KSF and cation exchange resin have also been reported [12-17], for this purpose. More recently, Chao-Jun Li et al. reported the synthesis of pyranoquinolines in water catalyzed by indium [18] chloride, and Johnson et al. reported a cation exchange resin-catalyzed synthesis of pyrano naphthyridine [18]. However, these reagents often lack selectivity in their reactions. However, in the quest for synthesizing these compounds, using an in situ generated heterodyne [19], is more favorable than employing preformed heterodienes. This preference arises because heterodienes [20] are inherently unstable, hygroscopic, and pose challenges in terms of purification through column chromatography. Consequently, there is a pressing need for an efficient, selective, and straightforward protocol for the synthesis of these compounds. Surprisingly, there have been no reports on the synthesis of pyrano/furanoquinolines [21-23] using an organo catalyst. Camphor sulfonic acid is a well-established acid catalyst in organic chemistry, actively participating in a wide array of reactions, including nucleophiles-promoted alkyne-iminium cyclization, intramolecular opening of epoxides, phenyl elation reactions, and spiroacetalization reactions. In this context, we present a highly diastereoselective method for synthesizing pyrano/furano naphthyridine [24-26]. This method involves the reaction of aromatic amines with cyclic enol ethers, catalyzed by camphor sulfonic acid as an organ catalyst, all conducted at ambient temperature.

Results and Discussion:

The reaction described herein is classified as an ABB' type multi-component reaction. This categorization arises from the unique behavior of the cyclic enol ether (B) component, which that, chemically differentiated into two distinct manners represented as (B and B'). The term "chemo differentiating" emphasizes that each chemical function

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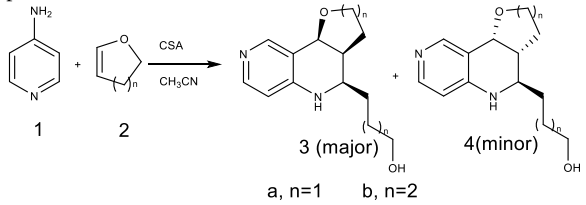
incorporated into the final product is chemically distinct from the other.

In this Multi component Povarov reaction, the cyclic enol ether serves a dual role. Firstly, it acts as an electron-rich dienophile, participating in the cycloaddition reaction. Secondly, it functions as an aldehyde in the formation of a Schiff base. The ABB' classification of this reaction highlights the dual functionality of component B (B and B'), underscoring its significance in ensuring the complexity and functional diversity of the resulting product Scheme1.



Scheme1. Synthesis of compounds **3** and **4**

The experimental procedure involved the reaction of 4-aminopyridine (1.0 mmol) with cyclic enol ether (2.0 mmol) in the presence of 30% CSA (Camphor sulfonic acid) in acetonitrile at room temperature. This reaction yielded the corresponding pyrano and furano naphthyridine compounds **3** and **4** in good to excellent yields.

The success of this reaction showcases the efficiency and selectivity of Camphor sulfonic acid as an organ catalyst in facilitating the diastereo selective synthesis of pyrano and furano naphthyridine derivatives. This methodology offers a valuable contribution to the synthesis of these complex and biologically relevant compounds.

In these reactions, both cis and trans isomers are formed in nearly all cases. However, the Camphor sulfonic acid-catalyzed reaction exhibits a preference for the formation of the cis isomer, showing high diastereoselectivity. Interestingly, furanoquinolines exhibit better diastereoselectivity compared to pyrano naphthyridine under these reaction conditions.

To optimize the reaction conditions and catalyst loading, aniline and 3,4-dihydro-2H-pyran were used as a model system. Initially, when 4-aminopyridine reacted with pyran in the presence of only 5 mole % Camphor sulfonic acid in CH_3CN, only a trace amount of the desired product was formed after 24 hours.

To determine the best reaction conditions, experiments were conducted with varying amounts of Camphor sulfonic acid, including 5, 10, 20, and 30-mole %. The most favorable results were obtained when using 30-mole % of Camphor sulfonic acid, resulting in improved yields and reduced reaction times. This optimization process underscores the importance of catalyst loading in achieving efficient and selective transformations in this synthetic protocol.

Blank reactions, conducted without a catalyst, involving aniline and 3,4-dihydro-2H-pyran at room temperature in CH_3CN for 3 days did not yield any observable reaction. This suggests the crucial role of the catalyst, specifically Camphor sulfonic acid (CSA), in facilitating the desired transformations.

The solvent's influence on the reaction also explored by conducting the reaction in various solvents, including acetonitrile, DMF, THF, THF/H_2O (7:3), and acetonitrile/H_2O (7:3). Acetonitrile found to be the most effective solvent in terms of both yields and reaction times. Interestingly, when water was added alongside acetonitrile and THF, the diastereo-selectivity shifted towards the trans isomer.

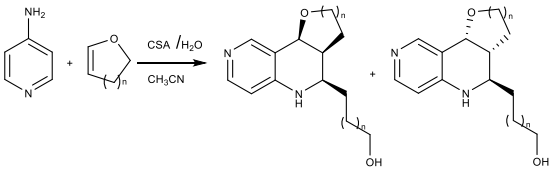
Several other catalysts, including Citric acid, tartaric acid, PTSA (p-toluenesulfonic acid), and CSA, were tested for their catalytic activity. CSA exhibited superior diastereo selectivity compared to the others, although PTSA showed relatively better results compared to citric acid and tartaric acid (**Table 1**).

Table-1: Reaction optimization with organ catalyst and solvent

Reaction condition: 1mmol (aromatic-amine) 2 mmol (cyclic enol ether) [a] isolated yield [b].

Organo-catalyst	Mole	Solvent	Time (h)	Yield (%)	cis/trans [b]
Citric acid	30%	CH_3CN	9	45	55:45
Tartaric acid	30%	CH_3CN	10	50	60:40
PTSA	30%	CH_3CN	8	60	65:35
CSA	0%	CH_3CN	48	-	-
CSA	5%	CH_3CN	24	trace	-
CSA	20%	CH_3CN	8	56	75:25
CSA	30%	THF	8	57	65:35
CSA	30%	DMF	8	52	63:27
CAS	30%	CH_3CN	4	80	85:15
CAS	30%	THF-H_2O	8	65	48:52
CAS	30%	DMF-H_2O	8	50	50:50
CAS	30%	CH_3CN-H_2O	4	80	35:65

The reaction described in this study involves the coupling of an electron-rich alkene (specifically, a cyclic enol ether) with 4-aminopyridine. This coupling process may proceed through two potential mechanisms: a concerted inverse electron-demand Diels-Alder mechanism or a stepwise "Mannich-like" pathway. Based on this mechanistic hypothesis as shown in figure 1, Camphor sulfonic acid was chosen as the catalyst to facilitate the 1:2 coupling of 4-aminopyridine with electron-rich alkenes, such as 3,4-dihydro-*2H*-pyran or 2,3-dihydrofuran, resulting in the formation of highly functionalized pyrano and furano naphthyridine.



1 **2** **3**(minor) **4**(major)

Scheme 2. Synthesis of compounds **3** and **4** in presence of water**.**

Under the optimized conditions, the reaction of 4-aminopyridine with 3,4-dihydro-2H-pyran in acetonitrile in the presence of Camphor sulfonic acid (30 mol%) yielded pyrano naphthyridine in good yield (80%) with

high cis selectivity. In this case, **3** (Cis product) was the major product, while **4** (Trans product) was obtained as the minor product Scheme 2. The assignment of the cis diastereomer was based on comparisons with similar compounds and analysis of H5-H6 and H7 coupling constants (typically J-H5-H6 = 5-7 Hz and J-H6-H7 = 6-7 Hz).

The optimized conditions for pyrano naphthyridine were also successfully applied for the synthesis of furano naphthyridine, resulting in better selectivity and yield compared to the corresponding pyrano naphthyridine. Subsequently, a series of substituted anilines were reacted with cyclic enol ether to produce 2-(hydroxyalkyl) pyrano and furano naphthyridine derivatives.

In order to further study, the finding of shifting diastereo selectivity with the use of water as co solvent, we have carried out several reactions in water–acetonitrile system. Interestingly in all the reaction diastereo selectivity is switched towards trans with the use of water as co solvent. (Table 2) The possible explanation of shift in diastereo selectivity may be because 2-hydoxy tetrahydropyran or 2-hydroxy tetrahydrofuran reacts with 4-aminopyridine in water–acetonitrile system instead of 3, 4-dihydropyran or 2, 3-dihydrofuran. We further performed reaction in LiCl, and Guanidinium chloride with water as co solvent. Lithium chloride is a salt which increases the hydrophobic effect i.e. "Salt Out'' as expected from this we get an increase diastereo selectivity as well as increase in rate of reaction. Guanidinium chloride decrease the hydrophobic interaction i.e. "Salt In'' does not increase the rate of reaction but side product was also formed.

Table-2: Camphor sulfonic acid catalysed synthesis of pyrano/furano naphthyridine in CH_3CN and Water system.

Compound	n	Time (h)	Yield[a] (%)	Trans/cis[b]
3	1	4.5	78	75:25
4	2	4	80	55:45

A proposed mechanism for the formation of furanoquinolines is given in figure 1.

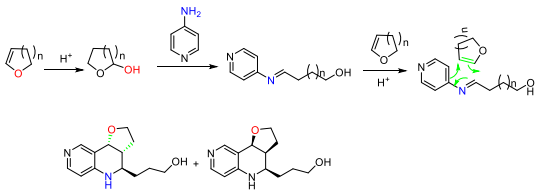


Figure 1. Proposed Mechanistic Pathway

Antibacterial activities

The antibacterial activity of the synthesized products pyrano naphthyridin and furano naphthyridin were tested *in vitro* against two bacterial *Staphylococcus aureus* as gram positive and *P. aeruginosa* as gram negative . Ampicillin was used as a reference standard antibacterial agent and the inhibition diameter values were presented in Table1. The compounds were dissolved in DMSO and the tests were carried out in triplicate. The data in Table 3 shown that the Staphylococcus aureus **5** pyrano naphthyridi recorded the highest antibacterial activity in which both isolate of the bacterial of were inhibited (IZ=0.18, 0.3 mm, respectively)[27]. (table 3, figure 2).

Table 3. Antibacterial activity of the tested compounds (pyrano naphthyridin and furano naphthyridin)

Compounds	Diameter of inhibition zone (IZ) / mm	
	Bacterial species	
	Staphylococcus aureus	*P. aeruginosa*
pyrano naphthyridin	0.18 ± 0.1	N
furano naphthyridin	0.3 ±0.4	N
Ampicillin	0.16 ±0.1	0.2 ±0.17

N = No effect

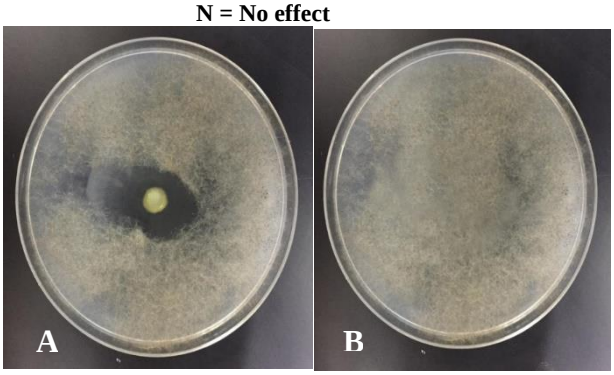


Figure 2. Effect of the tested compound (pyrano naphthyridin) on growth of *Staphylococcus aureus* cultivated in PDA medium after3 days at 27 °C in the dark. Inhibition zones represent the influence. (A) The filter paper disc embedding in pyrano naphthyridin, before culturing.(B) Control, the filter paper disc embedded before culturing

DOCKING STUDIES

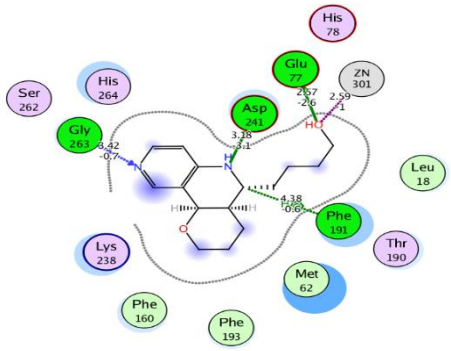
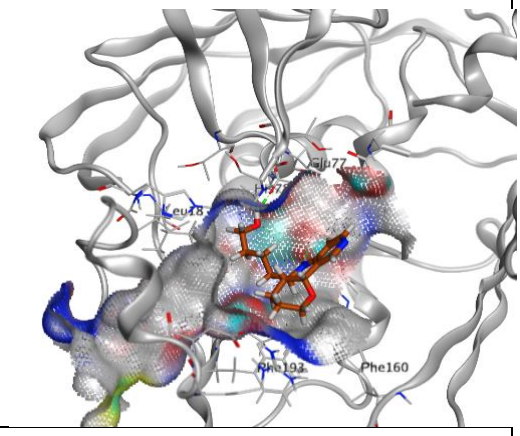
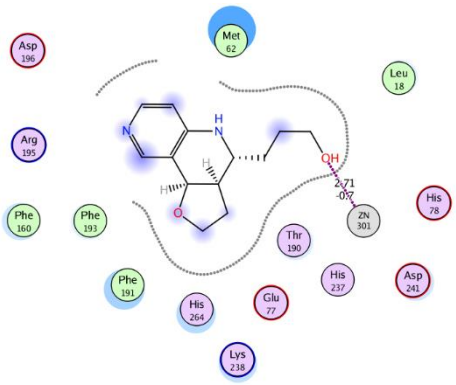
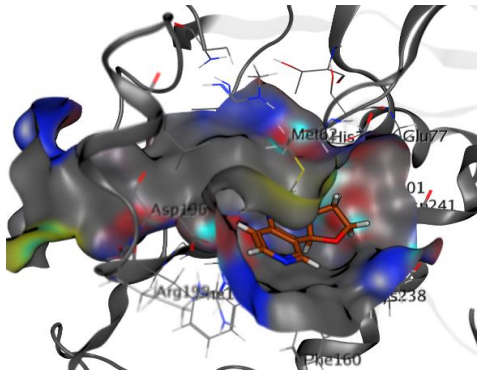
In order to have a better overview about the estimated binding interactions between the designed molecules (pyrano and furano naphthyridine) and various proteins, ligand-proteins docking of the assembled derivatives was studied. Proteins under investigation, namely; UDP-3-O-acyl-N-acetylglucosamine deacetylase(LpxC), was collected in the protein data bank (PDB: 7DEL) (http://www.rcsb.org). The Molecular Operating Environment (MOE®) version 2014.09 was used for this investigation. The types of molecular interaction results, molecular docking energy scores, and 2D and 3D interaction images of the assembled derivatives (pyrano and furano naphthyridine) and the protein are displayed in Tables 1 in the Supplementary Materials.

Table 2. Binding score of the newly prepared compounds and UDP-3-O-acyl-N-acetylglucosamine deacetylase(LpxC).

Compounds	S Score	RSMD	Interaction/bond type	Distance	E kcal/mol)
pyrano naphthyridine	-6.7381	2.2510	GLU 77 (A) H-donor ASP 241 (A) H-donor GLY 263 (A)H-acceptor 6-ring PHE 191(A) H-pi	2.57 3.18 3.42 4.38	-2.6 -3.1 -0.7 -0.6

furano naphthyridine	-5.2486	1.7788	HIS 78 (A) metal ASP 241 (A) ionic ASP 241 (A) ionic	1.86 1.92 2.47	-2.5 -17.9 2.47-

Table 3. The 2D and 3D interactions of ligands pyrano and furano naphthyridine against the active site of 7DEL.

Comp	2D	3D
Pyrano naphthyridin		
Furano naphthyridin		

Experimental Section:

The reactions were synthesis at room temperature, maintained between 28-32°C. Unless stated otherwise, all reagents were preparation from Sigma-Aldrich Chemical Co, Lancaster, and used directly without further purification. IR spectra were recorded using potassium bromide discs on a Bruker-Vector22 Fourier transform spectro- photometer located in Billerica.NMR spectra were acquired using a Brucker DPX 200 FT or Avance DRX 400MHz spectrometer, with chemical shifts (δ) reported in ppm relative to TMS and coupling constants (*J*) in Hz. Elemental analysis was carried out using a Perkin Elmer Auto system XL Analyzer. Melting points were determined using a COM-PLAB melting-point apparatus. Reactions monitored by thin layer chromatography (TLC). Mass spectra were detected at 70 eV using a Hewlett Packard spectrometer with model number MS-5988, situated in Palo Alto, CA.Elemental analyses were carried out at the Micro-analytical Center of Cairo University, Giza, Egypt.

Typical Experimental Procedure for the Synthesis of Pyrano/Furano naphthyridine:

A mixture comprising substituted 2-aminopyridine (1 mmol), cyclic enol ether (2 mmol), and Camphor sulfonic acid (30 mol %) was dissolved in acetonitrile (5 ml) and stirred at room temperature for 4–6 hours. Upon completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and then extracted with ethyl acetate. The organic phase was dried using Na_2SO_4, filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography to yield pure pyrano/furan naphthyridine derivatives. All the products were characterized using ^1H and ^{13}C- NMR spectroscopy.

Typical Experimental Procedure for the Synthesis of Pyrano/Furano naphthyridine in Biphasic System:

A mixture of 2-aminopyridine (1 mmol), cyclic enol ether (2 mmol), and Camphor sulfonic acid (30 mol %) was dissolved in a mixture of acetonitrile and water (5 ml, 7:3 ratio) and stirred at room temperature for 4–6 hours. After the reaction completed, as indicated by TLC (ethyl acetate :petroleum ether 4:1), the reaction mixture quenched with water and then extracted with ethyl acetate. The organic phase dried using Na_2SO_4, filtered, and concentrated under vacuum. The product purified by silica gel column chromatography to afford pure pyrano/furano

naphthyridine derivatives. All the products were characterized using ^{1}H and ^{13}C- NMR spectroscopy.

3-(-2,3,3a,4,5,9*b*-Hexahydrofuro[3,2-*c*][1,6]naphthyridin-4-yl)propan-1-ol (3a, 4a)

Viscous oil. **Compound 3(a) Cis-isomer:** IR (KBr), (cm^{-1}): 3109 (C-H aromatic), 3216 (NH). ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.55-1.90 (m, 5 H), 2.03 (m, 1 H), 2.64 (1 H, OH), 2.63 (m, 1 H), 3.44 (m, 1 H), 3.70 (m, 2 H), 3.79 (m, 2 H), 5.11 (d, *J* = 8.0 Hz, 1 H), 6.30 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.76 (m, 1 H, Ar-H), 7.04 (m, 1 H, Ar-H), 7.29 (d, J = 7.6 Hz, 1 H, Ar-H) ppm. ^{13}C-NMR (100MHz, CDCl3): δ = 24.22, 29.21, 30.93, 42.69, 52.68, 62.52, 66.81, 76.02, 114.86, 118.94, 122.84, 128.55, 130.25, 145.24 ppm. EIMS (234.) m/z: 234.04 (100.0%), 225.05 (14.2%), Analysis calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.62; H, 7.70; N, 11.93.

Compound 4(a) Trans isomer: ^{1}H NMR (400MHz, $CDCl_3$), δ: 1.50-1.90 (m, 5 H), 2.20 (m, 1H), 2.64 (1H, OH), 2.82 (m, 1 H), 3.70 (m, 2 H), 3.79 (m, 2 H), 3.95 (m, 1 H), 4.56 (d, *J* = 5.6 Hz, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.09 (m, 1H, Ar-H), 6.76 (m, 1 H, Ar-H), 7.34 (d, *J* = 7.6 Hz, 1 H, Ar-H) ppm.^{13}C NMR (100MHz, $CDCl_3$): δ = 28.79, 29.37, 30.09, 41.39, 52.16, 62.64, 65.76, 76.10, 115.08, 118.42, 120.48, 129.10, 131.20, 145.16 ppm. EIMS (234.) m/z: 234.04 (100.0%), 225.05 (14.2%), Analysis calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.62; H, 7.70; N, 11.93.

4-(-3,4,4a,5,6,10b-Hexahydro-2*H*-pyrano[3,2-*c*][1,6]naphthyridin-5-yl)butan-1-ol (3a, 4a)

Solid, mp 89–91°C. **Compound, 3b Cis-isomer.** IR (KBr), (cm^{-1}): 3107 (C-H aromatic), 3198 (NH).^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.32 - 1.70 (m, 10 H), 2.00 (dd, J = 3.0, 5.4, 7.1, 12.1 Hz, 1 H), 3.34 (dt, *J* = 2.2, 7.0 Hz, 1 H), 3.39 (dt, *J* = 2.3, 11.4 Hz, 1 H), 3.60 (ddt, *J* = 1.6, 4.4, 11.4 Hz, 1 H), 3.67 (t, *J* = 6.3 *Hz*, 2 H), 4.98 (d, J = 5.7 Hz, 1 H), 6.38 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.67 (t, J = 7.5 Hz, 1 H, Ar-H), 6.96 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.31 (d, *J* = 7.5 Hz, 1 H, Ar-H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.86, 22.14, 25.41, 31.96, 32.59, 35.52, 54.13, 60.63, 62.47, 72.41, 113.79, 117.74, 120.02, 127.51, 127.85, 145.01 ppm. EIMS (262) m/z: 262.17 (93.0%), 225.05 (32.2%), Analysis calcd. for $C_{15}H_{22}N2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.63; H, 8.40; N, 10.63.

Compound 4b Trans-isomer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 -1.70 (m, 10 H), 1.90 (m, 1 H), 3.58 (m, 1 H), 3.66 (m, 3 H), 3.90 (m, 1 H), 4.42 (d, *J* = 3.2 Hz, 1 H), 6.42 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.60 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.96 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.21 (d, *J* = 7.5 Hz, 1.H, Ar-H) ppm. EIMS (262) m/z: 262.17 (93.0%), 225.05 (32.2%), Analysis calcd. for $C_{15}H_{22}N2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.63; H, 8.40; N, 10.63.

Conclusion:

We have successfully developed a synthetic methodology for the preparation of pyrano and furano naphthyridine catalyzed by Camphor sulfonic acid. This method enables the highly diastereoselective synthesis of pyrano/furano naphthyridine by reacting 2-mainopyridine with cyclic enol ether using Camphor sulfonic acid as an organo catalyst at ambient temperature. Our proposed synthetic route not only offers an alternative approach to accessing naphthyridine moieties but also demonstrates a sustainable protocol for the synthesis of heterocyclic structures. The observed diastereoselectivity in this process is a pivotal feature of our developed methodology, enhancing its utility and efficiency in the synthesis of these valuable compounds.

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