International Journal for Research in Applied Sciences and Biotechnology

www.ijrasb.com

ISSN: 2349-8889
Volume-6, Issue-2 (March 2019)

Synthesis of Pharmaceutically Important Isoxazoles

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ABSTRACT

2-acetylnaphtho [2,1-b] furan has been synthesized by literature (Stoermer & Schaffer) method. It is then converted in to a series of Chalcones on treatment with p-substituted aromatic aldehyde. (1a-f) by Claisen-Schmidt condensation. These chalcones on reaction with Br_2 in presence of methanol and glacial acetic acid gave their dibromo derivative (2a-f). This product reacts with hydroxylamine hydrochloride in pyridine and methanol respectively to get isomeric isoxazoles (3a-f) and (4a-f). The antimicrobial screening showed that many of these synthesised compounds have good activity against bacteria and fungi.

Keywords- Naphthofuran, Pyridine, Chalcones, Isoxazoles.

I. INTRODUCTION

Survey of literature revealed the important of naphthofuran derivatives as biologically, pharmacologically and industrially important molecules (1,2). The napththofuran derivatives have been shown to exhibit cytotoxic activity. keeping these reports in view and in continuation of all search. For more potent napththofuran derivatives (3-5). For the biological and pharmaceutical importance of isoxazoles see: Basappa et. al (6-11). Nair and wadodkar have reported the synthesis of isomeric isoxazoles from 1-(2-furyl)-3-(2hydroxyphenyl)-1,3-propandione in pyridine and methanol respectively. Isoxazoles also have been synthesized from chalcone dibromide (12-13). Literature survey reveals that isoxazoles and their isomers have not been prepared. This prompted us to synthesize some isomeric isoxazoles from dibromo propane 1-one.

II. EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded in KBr on Bruker FT-IR (Alpha-p)^{1}H NMR spectra on Bruker "AVANCE 400" MHz spectrometer using TMS as a standard, (chemical shifts in δppm) and mass spectrum on Shimadzu GCMS QP 5050A. Japan model-DI mass spectrometer operating at 70ev. Progress of the reaction was monitored by TLC. The entire compounds have been recrystallized from ethanol.

Typical experimental procedure for synthesis of 3-(4-hydroxyphenyl)-1-(naphtho [2, 1-b] furan -2yl) prop-2-en-one.

Flask was charged with mixture of 2-acetylnaphto [2, 1-b] furan (4.20 gm,0.02 moles) (1) and p-hydroxy benzaldehyde (2.68 gm, 0.022 mol). It was stirred in ethanol (50 mL) and then potassium hydroxide (50%) (10ml) was added portion wise, keeping the temperature below 10^0C throughout the addition. The mixture was kept for 36 hr at room temp., after completion of reaction, reaction mixture was poured into crushed ice and the solid obtained was filtered under vacuum. It was washed firstly with sodium carbonate solution and then with water, dried and the product was recrystallized from ethanol to afford the pure product in 60-70% yield (1a-f). Same procedure is extended for other compounds of this series by using appropriate aldehyde. Yield 78% M.P.156^{O}C

Spectral discussion of synthesised 1-(naphtho[2,1-b]furan-2-yl)-3-(4-hydroxy) phenylprop-2-en-1-one)

IR (KBr, vcm^{-1}): 3310 cm^{-1}(Ar-o-H str.), 3058 cm^{-1}(-CH str. of. Ar), 1644 cm^{-1}(C=0 str. in ketone),1586 cm^{-1}(C=C str.) 1515 cm^{-1} (C=C str. in Ar), 1443 and 1359 cm^{-1} (CH_3 def.), 1153 and 1167 cm^{-1} (C-O-C str) 830 cm^{-1} (-CH str.) 747 cm^{-1} (Ar-H-opb)

^{1}H NMR (CDCl$_3$ in δ pmm): 6.35(d,lH-CO-CH), 6.95(d,lH, C=CH),7.21-8.24 (complex m, 11 H, Ar-protons),10.32 (s,1H, phenolic-OH) proton

Mass (m/z): 314[M]$^+$, 221, 195, 147, 119, 118, 91, 69, 65, 43

Synthesis of 2,3-dibromo-1-(naphtho[2,1-b]furan-2-yl)-3- substituted phenylpropan-1-one (2a-f)

A mixture of 1-(naphtho[2, 1-b]furan-2-yl)-3-phenyl prop-2-en-one (0.01 moles) (1a) was dissolved in glacial acetic acid by warming and solution was cooled. A solution of bromine in acetic acid (6.4ml 25% w/v) was added to this solution with stirring. After 15 minutes, the dibromide prepared was filtered and washed with little alcohol followed by petroleum ether to get (2a). Compounds (2 b-f) were prepared similarly from (1b-f). Yield 72 % M.P.178 ^{O}C

Spectral discussion of synthesised 2,3-dibromo-1-(naphtho[2,1-b]furan-2-yl)-3-substitutd 4-hydroxy phenylpropan-1-one

IR (KBr, vcm^{-1}) 3340 cm^{-1}(Ar-O-H str.), 3068 cm^{-1}(-CH str. of Ar), 1678 cm^{-1}(C=0 str. in ketone), 1535 cm^{-1} (C=C str. in Ar), 1453 and 1369 cm^{-1} (CH_3 def.), 1144 and 1132cm^{-1} (C-O-C str) 870 cm^{-1} (-CH str.) 787 cm^{-1} (Ar-H-opb),743 cm^{-1} (-C-Br str)

^{1}H NMR (CDCl$_3$ in δ pmm): 6.78(d,lH-CO-CH), 7.35(d,lH, C=CH),7.41-8.67 (complex m, 11 H, Ar-protons),10.77 (s,1H, phenolic-OH) proton.

Mass (m/z) : 474[M]$^+$, 289,210,185,94

Synthesis of 3-(naphtho[2,1-b]furan-2-yl)-5- substituted phenylisoxazole (3a-f)

A mixture of 2,3-dibromo-1-(naphtho[2,1-b]furan-2-yl)-3-phenylpropan-1-one (2a-f) (0.01 moles) and hydroxylamine hydrochloride (0.012 moles) in pyridine (20ml) was refluxed for 3hr. contents were cooled, diluted with water and acidified with 1:1 HCL. The crude product thus obtained was crystallised from ethanol to get (3a-f). Yield 68 % M.P.207^{O}C

Spectral discussion of 3-(naphtho[2,1-b]furan-2-yl)-5-substituted 4-hydroxy phenyl isoxazole (IR (KBr, vcm^{-1}): 3160-3130 cm^{-1}(Ar-O-H str.),1621 cm^{-1} (C=C str. in Ar), 1578 (C=N str.) 970-946 cm^{-1} (C=N –O str), 887-843 cm^{-1} (2'furyl)

^{1}H NMR (CDCl$_3$ in δ pmm): 7.71-8.97 (complex m, 11 H, Ar-protons), 7.77 (aromatic proton of isoxazole), 10.77 (s,1H, phenolic-OH) proton.

Mass (m/z) : 327[M]$^+$, 235,168,163,94.

Synthesis of 5-(naphtho[2,1-b]furan-2-yl)-3-substituted phenyl isoxazole (4a-f)

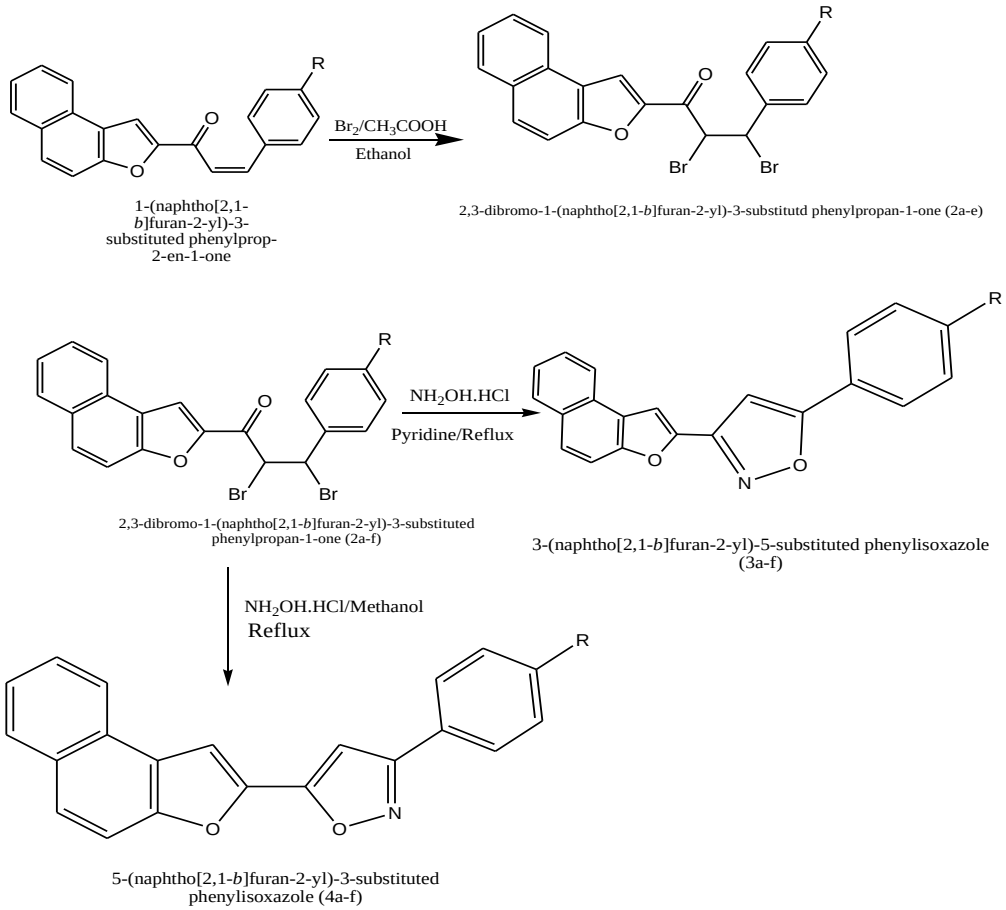
A mixture of 2,3-dibromo-1-(naphtho[2,1-b]furan-2-yl)-3-phenylpropan-1-one (2a-f) (0.01mole) and hydroxylamine hydrochloride (0.012 moles) in methanol (20 ml) refluxed for 5hr. further it was cooled to obtain the product which was crystallized from ethanol to get the compound 5-(naphtho[2,1-b]furan-2-yl)-3-phenylisoxazole (4a-f). Other members of the series were synthesized in similar manner. Yield 62 % M.P.223 ^{O}C

Spectral discussion of 5-(naphtho[2,1-b]furan-2-yl)-3-substituted hydroxyl phenylisoxazole (IR (KBr, vcm^{-1}): 3168-3143 cm^{-1}(Ar-O-H str.),1632 cm^{-1} (C=C str. in Ar), 1589 (C=N str.) 984-966 cm^{-1} (C=N –O str), 897-832 cm^{-1} (2'furyl)

^{1}H NMR (CDCl$_3$ in δ pmm): 7.41-8.87 (complex m, 11 H, Ar-protons), 7.82 (aromatic proton of isoxazole), 10.61 (s,1H, phenolic-OH) proton.

Mass (m/z): 327[M]$^+$, 235,168,163,94.

Reaction Scheme



1-(naphtho[2,1-*b*]furan-2-yl)-3-substituted phenylprop-2-en-1-one

2,3-dibromo-1-(naphtho[2,1-*b*]furan-2-yl)-3-substitutd phenylpropan-1-one (2a-e)

2,3-dibromo-1-(naphtho[2,1-*b*]furan-2-yl)-3-substituted phenylpropan-1-one (2a-f)

3-(naphtho[2,1-*b*]furan-2-yl)-5-substituted phenylisoxazole (3a-f)

5-(naphtho[2,1-*b*]furan-2-yl)-3-substituted phenylisoxazole (4a-f)

Where R=H,CH_3,OH,OCH_3,Cl and F

ISSN: 2349-8889
Volume-6, Issue-2 (March 2019)

Table 1: Physical and characterization data of the synthesized compounds

Code	Molecular formula	Mol. weight	Yield	M.Pt. ℃	Elements % calc (found)			
					C	H	N	X
4a	$C_{21}H_{13}NO_2$	311	70	220	81.01 **(80.0)**	4.21 **(4.25)**	4.50 **(4.35)**	-------
4b	$C_{22}H_{15}NO_2$	325	72	232	81.21 **(81.0)**	4.65 **(4.50)**	4.30 **(4.22)**	-------
4c	$C_{21}H_{13}NO_3$	327	72	238	77.05 **(76.0)**	4.00 **(4.10)**	4.28 **(4.20)**	--------
4d	$C_{22}H_{15}NO_3$	341	74	248	77.41 **(77.50)**	4.43 **(4.30)**	4.10 **(4.05)**	--------
4e	$C_{21}H_{12}ClNO_2$	345	71	262	72.94 **(71.80)**	3.50 **(3.40)**	4.05 **(3.90)**	10.25 **(10.30)**
4f	$C_{21}H_{12}FNO_2$	329	70	270	76.59 **(76.87)**	3.67 **(3.96)**	4.25 **(4.37)**	5.77 **(5.89)**

Table 2: Antimicrobial activity of synthesized compound.

Comp	Antibacterial activity (zone of inhibition in mm)				Antifungal activity			
	E.coli	*S.typhi*	*S.aureus*	*B.substilis*	*A.niger*	*P.chryso-genum*	*F.moneli forme*	*C.albicans*
4a	13	18	17	20	+ve	+ve	+ve	-ve
4b	15	19	29	23	-ve	+ve	+ve	+ve
4c	17	18	24	21	+ve	+ve	+ve	+ve
4d	15	19	31	24	+ve	+ve	+ve	-ve
4e	11	12	10	08	-ve	-ve	+ve	-ve
4f	13	10	12	22	-ve	+ve	+ve	-ve
Pencillin	19	21	33	29	-	-	-	-
Griseofulvin	-	-	-	-	+ve	+ve	+ve	+ve

III. RESULT AND DISCUSSION

In this context we have reported that the facile synthesis of different 5-(naphtho[2,1-b]furan-2-yl)-3-substituted hydroxyl phenyl isoxazole derivatives in moderate to good yields. We hope this methodology will be helpful for further synthesis of different isoxazoles derivatives for pharmaceutical use. In the antimicrobial study, filter paper; disc diffusion plate method was employed to evaluate the antimicrobial activity. The zone of inhibition was compared with the standard drug. (Penicillin for bacteria and Griseofulvin for fungi). Results are summarized in Table 2. Investigation of antimicrobial activity revealed that the compounds (4a-f) showed significant antibacterial activity when compared with standard drug penicillin. However, the compounds (4b, 4c, 4d) were found to be more potent on all the bacterial strain. Compound (4a-f) showed significant antifungal activity when compared with standard drug Griseofulvin. Compound (4a, 4b, 4c, 4d) showed good antifungal activity. This result clearly revealed the contribution of electron releasing groups on the aromatic ring in enhancing the microbial activity.

REFRENCES

[1] V.P. Vaidya, C.S. Shreedhara, M. Gopal, M.S. Shahabuddin and P.S. Shenoy (2003), Evaluation of some novel heterocyclic compound for antifertility, antiinflamatory and analgesic activity, *Indian J. Pharm. Sci*. 65(6),580.

[2] V.P. Vaidya, K.M. Mahadevan and H.M. Vagdevi(2003), Synthesis of novel napththo[2,1-b]Furopyrimidine derivatives, *Indian J. Chem*. 42(B), 1931

[3] G.K.Nagraja, M.N.Kumarswamy, V.P.Vaidya, K.M.Mahadevan (2006) Microwave assisted synthesis of naphtho[2,1-b]furan-1,3,4-benzotriazepines: A potent antimicrobial agent, ARKIVOC 10,211

[4] H.M.Vagdevi, V.P.Vaidya, K.P.Latha, B-Padmashali (2006) Synthesis and pharmacological examination of some thiazolidinone derivatives of naphtho(2,1-b)furan, *Indian J. Pharm. Sci. 68,719*

[5] B. Padmshali, V.P. Vaidya, K.M. Mahadevan, K.P. Latha(2005) Synthesis of novel angularity fused pentacyclic heterocycles of pharmacological interest. *Indian J. Chem*. 44 (B), 1446

ISSN: 2349-8889
Volume-6, Issue-2 (March 2019)

[6] Y.Lee, S.M.Park and B.H.Kim(2009) Synthesis of-5-isoxazole-5-yl 2^1-deoxyuridine exhibiting antiviral activity against HSV and several RNA viruses, Bioorg.med.chem.lett.19,1126-1128.

[7] M.P.Basappa, K.Sadashiva, S.Mantelingu, S.Nanjunda, K.S.Rangappa(2003), Solution-phase Synthesis of novel Δ^2-isoxazoline libraries via 1,3-dipolar cycloaddition and their antifungal properties, Bioorg. Med. Chem. Lett. 11,21,4539-4544.

[8] M.Zia, S.Hameed, I Ahmad, N.Tabassum, S.Yousuf(2020), Regino-isomeric isoxazole,sulfonates: Synthesis, characterization, electrochemical studies and DNA binding activity, J.Mole.Structure,1220,128635

[9] S.S.Thakare, A.G.Doshi(2001), A novel synthesis of some isomeric isoxazoles, Asian J. of Chem.13(2)780-782

[10] L.Chen, Z.Wang, H.Lin, Xinyne Li&B.Wang(2022), Tert. Butyl nitrite triggered radical cascade reaction for synthesizing isooxazoles by a one pot multicomponent strategy, Chem.Commun.58,9152-9155.

[11] R.G.Micetich(1970), Studies in isoxazole chemistry. IV Isoxazoles via isoxazolines. Canadian J.Chem.,48,3753.

[12] R.P.Barncs and A.Brandon (1943), The properties of p-methoxydibenzoylmethane, J.am. Chem. Soc. 65,1070-1072

[13] A.Shaik, R.R.Bhandare, K.Palleapati, S.Nissan Kararao, V.Kancharlapalli, S.Shaik(2020), Antimicrobial,antioxidant and anticancer activities of some novel isoxazole ring containing chalcone and dihydropyrazole derivatives, molecules 25(5),1047