Research Journal of Chemical Sciences _____ ISSN 2231-606X
Vol. **5(7),** 8-11, July **(2015)** *Res. J. Chem. Sci.*

A Novel Bromonaphthyl Based 2-Amino-1,3-Thiazines: Synthesis, Characterization with Invitro Antimicrobial Screening

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Available online at: www.isca.in, www.isca.me
Received 16th June 2015, revised 23rd June 2015, accepted 15th July 2015

Abstract

A clinically important substrate of bromosubstituted acetylnaphthalene was used as the precursor for the preparation of a series of 1-(2-bromonaphthalen-6-yl)-3-phenylprop-2-en-1-ones. The formed unsaturated ketones on treatment with thiourea in the presence of base like KOH in alcohol yields corresponding 4-(2-bromonaphthalen-6-yl)-6-phenyl-6H-1,3-thiazin-2-amine. The synthesized thiazines are evaluated their structure on the basis of NMR, MASS, IR and Elemental analyses along with their physical data. The antibacterial and antifungal activities indicate some of these thiazines are potential antimicrobial agents.

Keywords: Synthesis, bromonaphthalene, 2-amino-1,3-thiazines, characterization, antimicrobial screening.

Introduction

Thiazine core having great interest in recent years especially in synthetic drug formulation in vowing with their proved biological activities[1]. Aminothiazines with amino group occupying the position in between two hetero atoms are important synthetic target as well as building block of various heterocycles. These substituted 2-amino-1,3-thiazines are proved to be very potent antimicrobial[2], antiinflammatory[3], antihypertensive[4], calcium channel blocker[5] etc. Bioactive molecules with bromo substitution are key intermediates for the synthesis of biologically active molecules[6] and are antimicrobials[7].

The amino thiazines are synthesised from various methods especially from chalcones. The chalcones are α,β-unsaturated ketones posses a wide range of biological activities such as antibacterial, antiviral, analgesic etc[8,9]. In addition with these observations, the substituted naphthalenes show a variety of biological activities such as antitumour[10], antifungal[11] etc. By focusing the importance of aminothiazines, substituted naphthalenes and bromo substitutions, along with our earlier work extension, we wish to synthesize the hybrid molecule of thiazine comprising with bromosubstituted naphthalene moiety.

Material and Methods

All the chemicals were analytical grade and solvents were distilled before use. Melting points of all the synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and are uncorrected. The purity of the compounds was checked by TLC using silica gel G. The IR spectra were recorded on SHIMADZU FT-IR spectrometer using KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker (AMX-400 MHz) using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm). Mass spectra were recorded on CLASS-5000 Mass spectrometer and elemental analyses were done on vario EL.CHNO elemental analyser.

Procedure for preparation of 1-(2- bromonaphthalen-6-yl)ethanone: The titled compound was prepared by the acetylation of 2-bromonaphthalene using acetylchloride in nitrobenzene in the presence of anhydrous aluminium chloride[12].

General procedure for preparation of 1-(2-bromonaphthalen-6-yl)-3-aryl prop-2-en-1-ones 3a-e: Quantitative amounts of substituted aromatic aldehyde (0.02 mol) and 1-(2-bromonaphthalen-6-yl)ethanone (0.02 mol) in ethanol (50 mL),were heated over a water bath while a solution of sodium hydroxide (1.5g in 5mL of water) was added slowly during 15 minutes and the heating was continued for further 15 minutes. The solution was cooled, filtered the product and recrystallised from ethanol.

General procedure for preparation of 2-amino-4-(2-bromonaphthalen-6-yl)- 6-aryl-6H-1,3-thiazines 4a-e: A solution containing 1-(2-bromonaphthalen-6-yl)-3-arylprop-2-en-1-one (0.01mol), thiourea (0.01 mol) and KOH (0.02 mol) in ethanol (50 mL) was refluxed for 4-5 hours and the reaction was monitored by TLC. After completion of the reaction, one third of the solvent was removed under reduced pressure, cooled to room temperature, poured to ice cold water and filtered the solid product. The pure 1,3-thiazines were obtained by column chromatographic technique using benzene-ethyl acetate as eluting solvent.

2-amino-4-(2-bromonaphthalen-6-yl)-6-phenyl-6H-1,3-thiazine 4a: Yield: 78%, M.P°C: 135; IR (KBr, cm^{-1}) 3351,

1525, 1362, 1285, 667 ^{1}H NMR, (δ, ppm): 4.24 (dd, 1H, $J_{1,2}$= 5.5Hz,$J_{1,3}$= 8Hz), 4.67 (dd, 1H, $J_{1,2}$= 2Hz,$J_{1,3}$= 14Hz), 8.42 (s, 1H), 8.46 (s, 1H) and 7.28-8.60 (m, 11H), ^{13}C NMR (δ, ppm): 45.01 (C-6), 106.60 (C-5), 134.80 (C-4), 167.77 (C-NH_2) 122.85-134.73 (Ar-C).

2-amino-4-(2-bromonaphthalen-6-yl)-6-(2-chlorophenyl)-6H-1,3-thiazine 4b: Yield: 80%, M.PºC: 140; IR (KBr, cm^{-1}) 3404, 1558, 1382, 1350, 669; ^{1}H NMR, (δ, ppm): 5.46 (dd, 1H, $J_{1,2}$= 2Hz,$J_{1,3}$= 4Hz), 5.79 (dd, 1H, $J_{1,2}$= 2 Hz,$J_{1,3}$= 4 Hz), 7.87 (s, 1H), 7.90 (s, 1H) and 7.26-8.0 (m, 10H), ^{1}H NMR (D_2O) 5.49 (d, 1H), 5.80 (d, 1H) 7.87 and 7.90 signals disappeared. ^{13}C NMR (δ, ppm): 53.70 (C-6), 99.49 (C-5), 138.89 (C-4), 176.13 (C-NH_2) 121.26-134.61 (Ar-C). Mass: m/z 429(M^+), 431(M^{+2}).

2-amino-4-(2-bromonaphthalen-6-yl)-6-(4-methoxyphenyl)-6H-1,3- thiazine 4c: Yield: 84%, M.PºC: 120; IR (KBr, cm^{-1}) 3320, 1531, 1389, 1315, 680; ^{1}H NMR, (δ, ppm): 5.29 (dd, 1H, $J_{1,2}$= 1Hz,$J_{1,3}$= 3.5Hz), 5.34 (dd, 1H, $J_{1,2}$= 1Hz,$J_{1,3}$= 3.5Hz), 7.88 (s, 1H), 7.90 (s, 1H) and 6.90-8.01 (m, 10H), ^{1}H NMR (D_2O) 5.33 (d, 1H), 5.29 (d, 1H) 7.88 and 7.90 signals disappeared. ^{13}C NMR (δ, ppm): 56.81(C-6), 101.80 (C-5), 134.53 (C-4), 175.21 (C-NH_2) 121.13-134.38 (Ar-C) 55.39 (O-CH_3). Mass: m/z 424(M^+), 426(M^{+2}).

2-amino-4-(2-bromonaphthalen-6-yl)-6-(4-methylphenyl)-6H-1,3-thiazine 4d: Yield: 75%, M.PºC: 145; IR (KBr, cm^{-1}) 3327, 1566, 1350, 1274, 651; ^{1}H NMR, (δ, ppm): 5.28 (broad s, 2H), 8.01 (s, 1H), 8.02 (s, 1H) and 7.28-8.55 (m, 10H). ^{13}C NMR (δ, ppm): 52.00 (C-6), 104.15 (C-5), 135.54 (C-4), 166.33 (C-NH_2), 121.24-135.36 (Ar-C), 21.44 (Ar-CH_3).

2-amino-4-(2-bromonaphthalen-6-yl)-6-(4-bromophenyl)-6H-1,3-thiazine 4e: Yield: 79%, M.PºC: 132; IR (KBr, cm^{-1}) 3396, 1560, 1327, 1273, 671; ^{1}H NMR, (δ, ppm):5.48 (dd, 1H, $J_{1,2}$= 2.5Hz,$J_{1,3}$= 4.5Hz), 5.77 (dd, 1H, $J_{1,2}$= 2Hz,$J_{1,3}$=4.5Hz), 8.01 (broad s, 2H), and 7.01-7.89 (m, 10H). ^{13}C NMR (δ, ppm): 56.06 (C-6), 99.65 (C-5), 134.59 (C-4), 176.00 (C-NH_2), 121.24-134.46 (Ar-C).

Antimicrobial activity: The synthesized compounds (**4a-e**) were screened for their invitro antimicrobial activity by using Mueller-Hinton broth method. Antibacterial activities were screened against three gram positive bacterias (*Bacillus subtillis, staphylococcus aureus and streptococcus pyogenes*) and three gram negative bacterias (*Escherichia coli, Klebsiella pneumoniae and pseudomonas aeruginosa*). Antifungal activities were screened against *Aspergillus flavus*, *Aspergillus niger* and *Penicillium chrysogenum.* Both antibacterial and antifungal activities were studied by measuring the zone of inhibition on agar plates at concentration 10µg/mL and reported in table-1. Ciprofloxacin used as the standard for antibacterial and amphotericin-B used as the standard for antifungal activities respectively.

Results and Discussion

The Friedal-Crafts acylation of 2-bromonaphthalene in the presence of a Lewis acid like anhydrous aluminium chloride in nitrobenzene affords 2-acetyl-6-bromonaphthalene and 1-acetyl-7-bromonaphthalene. The 2-acetyl-6-bromonaphthalene is purified by using literature method and undergoes Claisen-Schmidt condensation with equal molar ratio of substituted aromatic aldehydes in the presence of alkali metal hydroxides gives corresponding 1-(2-bromonaphthalen-6-yl)-3-arylprop-2-en-1-ones (3a-e). On further treatment of (3) with thiourea at reflux in ethanol containing potassium hydroxide gives the bromonaphthylthiazine derivatives (4a-e) (scheme-1). The formation of thiazine follows the Michael type addition of thiourea to α,β-unsaturated ketone and cyclisation.

The NMR spectra of all the synthesized compounds are confirmed the structure of thiazine in addition with the evidences obtained from IR, Mass and Elemental analyses (table-2). The physical parameters like TLC and Melting points (table-2) of synthesized compounds are quite different from starting materials also support the thiazine formation.

The compounds were evaluated for their antimicrobial activity. Most of the compounds exhibit good to moderate antibacterial and antifungal activities against the tested micro organisms. The compounds 4a and 4c shows better antifungal activity than the standard amphotericin-B against *Aspergillus flavus, Penicillium chrysogenum and Aspergillus niger* while the remaining compounds are inactive against fungi.

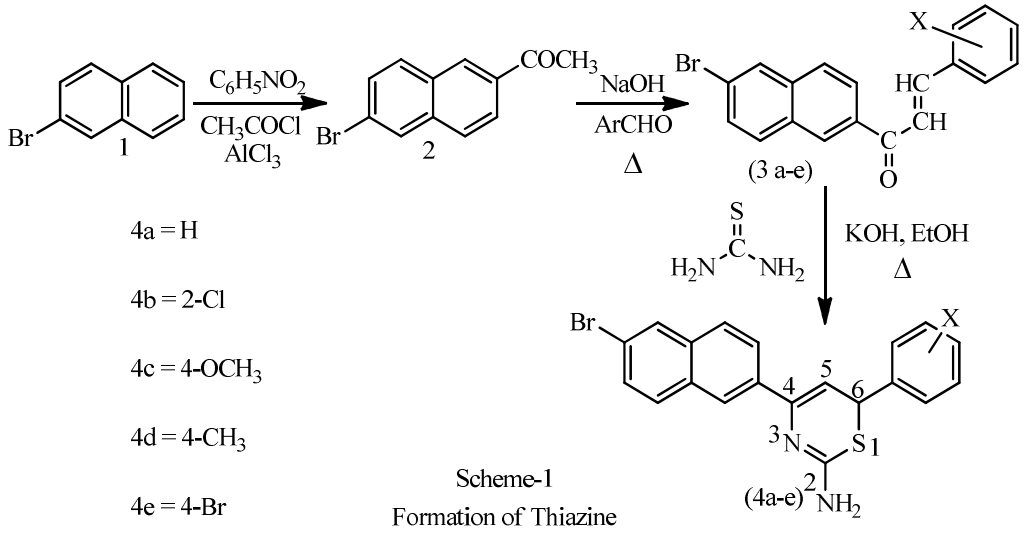
All the synthesized compounds are active against gram positive as well as gram negative bacterias but the antibacterial activity of these compounds are less and moderate as compared to standard *Ciprofloxacin*. Among these thiazines, the thiazines 4c and 4e shows slightly higher activity against gram positive bacterias. Among all bacterias, the compounds are more active against *Klebsiella pneumoniae*.

The ^{1}H NMR spectra of compounds 4a-e, having the characteristic signal for amino protons at the chemical shift value (δ, ppm) of 7.8-8.5 as two singlets for two protons. This separate signals arising due to the different orientation of amino protons with different hetero atoms viz. nitrogen and sulphur and this is confirmed by the addition of D_2O, results the disappearance of respective peaks at particular chemical shift values. The H-5 and H-6 protons are resonates in the aliphatic region with chemical shift values from 4.24-5.79 ppm as two separate doublet of doublets. These protons are undergoes long range coupling with nearest amino proton results doublet of doublets ($J_{1,2}$= < 3.0 Hz and $J_{1,3}$= > 3.5 Hz) (or) broad signals. The influence of amino protons in long rang coupling is confirmed by the reduced multiplicity of H-5 and H-6 protons as doublets instead of doublet of doublet or broad signals with the addition of D_2O. The aromatic protons show their characteristic multiplets in the regions of 6.9-8.6 ppm.

Table-1
Antimicrobial activities of compounds 4a-e (Diameter of inhibition in mm)

Compounds	Gram Positive Bacteria			Gram negative Bacteria			Fungi		
	A	B	C	D	E	F	G	H	I
Standard	16	21	17	20	19	22	11	10	11
Control	-	-	-	-	-	-	-	-	-
4a	9	9	10	7	10	8	18	19	13
4b	8	9	11	9	12	8	-	-	-
4c	13	10	8	7	11	12	15	11	14
4d	11	8	8	9	12	9	-	-	-
4e	8	11	9	8	8	8	-	-	-

A-*Bacillus Subtillis*, B-*Staphylococcus aureus*, C-*Streptococcus pyogens*, D-*Escherichia coli*, E-*Klebsiella pneumoniae*, F-*Pseudomonas aeruginosa*, G-*Aspergillus flavus*, H-*Aspergillus niger*. I-*Penicillium chrysogenum*



Scheme-1
Formation of Thiazine

Scheme-1
Formation of Thiazine

Table-2
Physical and analytical data of 4a-e

Compounds	Melting Point (ºC)	Yield (%)	Molecular Formula	Elemental Analysis		
				Carbon found (Cal cd) %	Hydrogen found (Cal cd) %	Nitrogen found (Cal cd) %
4a	135	78	$C_{20}H_{15}BrN_2S$	60.76 (60.92)	3.79(3.92)	7.08(7.19)
4b	140	80	$C_{20}H_{14}BrN_2SCl$	55.94 (55.99)	3.26(3.33)	6.52(6.66)
4c	120	84	$C_{21}H_{17}BrN_2SO$	59.29 (59.62)	4.00(4.18)	6.58(6.72)
4d	145	75	$C_{21}H_{17}BrN_2S$	61.61 (61.82)	4.15(4.31)	6.84(6.97)
4e	132	79	$C_{20}H_{14}Br_2N_2S$	50.63 (50.77)	2.95(2.81)	5.90(5.99)

*The values within the paranthesis are calculated value.

The ^{13}C NMR displays characteristic peaks at (δ, ppm) 45-56 (C-6), 99-106 (C-5), 134-138 (C-4), 166-176 (C-NH_2), 121-135 (C-Ar). The IR spectra of compounds shows the characteristic bands (cm^{-1}) corresponding -C-Br stretching (650-700), C=N stretching (1550-1570), -C-NH_2 stretching (1300-1400), -NH stretching (3300-3500) and -C-S stretching (1200-1400). The Mass spectra of compounds 4b and 4c shows the corresponding fragmented ions and molecular ion peaks, M^+ (424 and 429), M^{+2} (426 and 431).

Conclusion

In the present work, we have synthesized a series of 2-amino-4-(2-bromonapthalen-6-yl)-6-phenyl-6H-1,3-thiazines from the corresponding 1-(2-bromonapthalen-6-yl)-3-arylprop-2-en-1-ones and evaluated their antibacterial and antifungal activities in invitro conditions. The synthesized compounds are

characterised by using spectral (IR, NMR and Mass), elemental and physical (Melting points and TLC) techniques.

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