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Note

Synthesis and antimicrobial activity of 3-propene 1,2-benzisoxazole derivatives

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A convenient and eco-friendly synthesis of 3-propene 1,2-benzisoxazole derivatives **5a-h** has been achieved in excellent yields from the corresponding substituted *o*-hydroxy aceto-phenones. Substituted *o*-hydroxy acetophenones **1a-h** on treatment with acetaldehyde **2** in sodium hydroxide afford 1-(2′-hydroxy aryl)-2-butene-1-ones **3a-h**. Compounds **3a-h** on oximation yields **4a-h**. Microwave irradiation of **4a-h** on solid support silica gel affords **5a-h** in very good yield. The resultant 3-propene 1,2-benzisoxazoles have been characterized by spectral data. The compounds **5a-h** have been screened for their antimicrobial activity. Compounds **5b, d, e, g** exhibit good antibacterial activity and compounds **5b-e** exhibit marked antifungal activity.

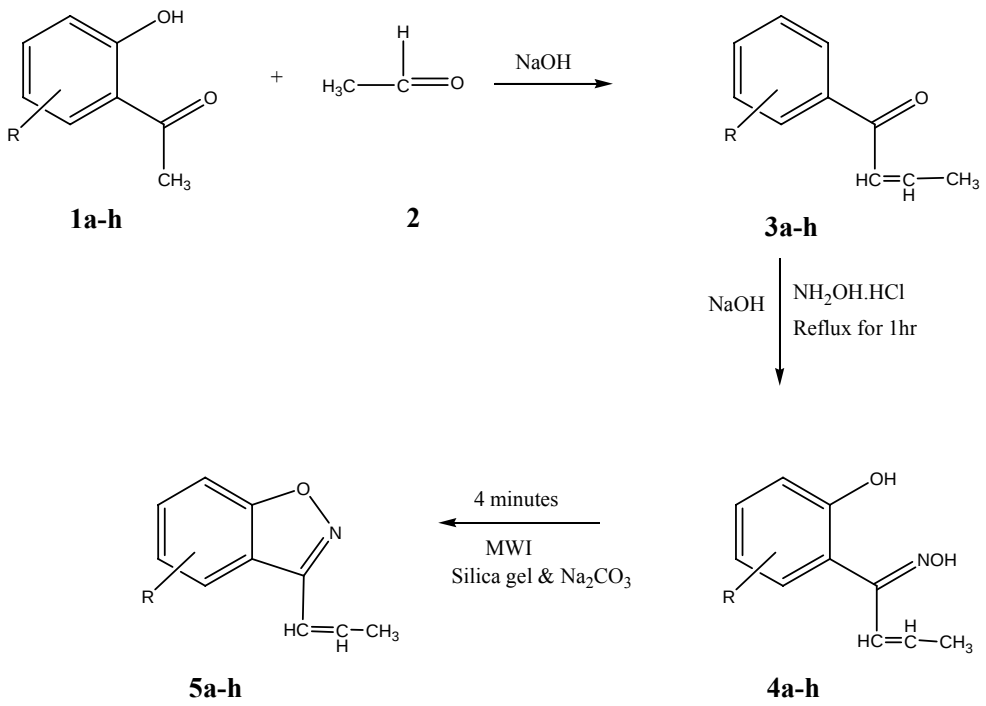
Keywords: 3-Propene, 1,2-benzisoxazole, microwave irradiation, antimicrobial activity

1,2-Benzisoxazoles have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as analgesic[1], anti-convulsant[2,3], antipsychotic[4,5], and as antimicrobial[6] agents. Further our earlier work showed significant activities in 3-substituted 1,2-benzisoxazole[7] derivatives. In view of the diverse type of biological activity it was thought worthwhile to prepare the title compound with the hope that propene substituent at three positions may prove to be biologically active and evaluate them for antimicrobial activity. The results of these studies are presented in this paper.

Results and Discussion

In the present investigation 1-(2′-hydroxy aryl)-2-butene-1-one **3a-h** have been prepared by the Claisen Schmidt condensation, of substituted *o*-hydroxy acetophenone **1a-h** and acetaldehyde **2** by the known literature method[8]. Their IR spectra show the stretching frequency for α,β unsaturated keto group near to 1650 cm^{-1} and –OH near 3400 cm^{-1}. The desired **4a-h** 1-(2′-hydroxy aryl)-2-butene-1-oxime were prepared by oximation of **3a-h** by using hydroxylamine hydrochloride and sodium hydroxide. The IR spectra of **4a-h** revealed the presence of =NOH in the region 3350-3300 cm^{-1} and the absence of absorption band due to >C=O at 1650 cm^{-1}. This is further supported by ^{1}H NMR which shows the presence of oxime –OH peak in the region δ 1.25-1.8 and phenolic OH from δ 11.25-12.00 and presence of alkene protons in the region δ 6.83-7.26. Compounds **4a-h** were soluble in sodium hydroxide with positive ferric chloride test and negative 2,4-dinitrophenyl hydrazine test and positive Lassaigne's test for nitrogen. The chemical and spectral evidences explains structure of **4a-h** as 1-(2′-hydroxy aryl)-2-butene-1-oxime. The desired **5a-h** 3-propene 1,2-benzisoxazole derivatives were prepared by microwave irradiation. The reaction of **4a-h** with sodium carbonate adsorbed silica gel (60-120 mesh), under solvent free microwave irradiation[9] afforded **5a-h**. The reaction was completed in 4 min with 100% power at 2450 MHz with recovery of product in high yield (**Scheme I**). Compounds **5a-h** were insoluble in dilute solution of NaOH and did not give coloration with neutral ferric chloride indicating the involvement of 2′-hydroxy group in cyclization. These compounds also gave Bayer's test positive for ethylenic double bond. IR spectra shows the absence of band due to =NOH. A strong band near 1530-1550 cm^{-1} indicates the presence of >C=N of isoxazole ring. ^{1}H NMR shows the absence of OH peak in the region δ 11-12 and absence of =NOH peak in the region δ 1.25-1.5. It also shows the presence of ethylenic double bond, a peak in the region δ 7.6 (s, H, -CH_A=CH) and δ 2.3-2.8 (q, 1H, -CH=CH_B). The later alkene proton was shielded because of the unshared pair of electrons on the nitrogen which is involved in the conjugation[10]. On the basis of chemical reactions and spectral data structure of **5a-h** can be assigned as 3-propene-1,2-benzisoxazole derivatives.

In conclusion, a new and convenient synthesis of 3-propene 1,2-benzisoxazole derivatives has been developed which is found to be simple, high yielding with high purity of product.



Scheme I

Experimental Section

All melting points were determined in open capillaries and are uncorrected. The homogeneity of all the compounds was checked by TLC on silica gel coated plates. IR spectra (KBr) were recorded on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on 300 MHz instrument using TMS as internal standard (chemical shift in δ, ppm).

General procedure for the preparation of 1-(2′-hydroxy aryl)-2-butene-1-ones, 3a-h

A mixture of substituted *o*-hydroxy acetophenone (0.01 M) and acetaldehyde (20% 0.04 M) was dissolved in 10 mL ethanol. To this mixture 10 mL of 40% KOH was added, the reaction-mixture was stirred and kept at RT for 24 hr. Then the reaction- mixture was poured over crushed ice and contents were acidified with concentrated hydrochloric acid. Product thus obtained was purified by recrystallization from 75% acetic acid. Their characteristic data are given in **Table I**.

General procedure for the preparation of 1-(2′-hydroxy aryl)-2-butene-1-oxime, 4a-h

Compound **3** (0.01 M) was dissolved in 10 mL of ethyl alcohol. To this 0.05 M of sodium hydroxide (in 10 mL water) and 0.015 M of hydroxylamine hydrochloride (in 10 mL water) were added. Contents were refluxed for 1 hr and the reaction-mixture was left overnight. Mixture was poured in cold water and contents were acidified with hydrochloric acid. Product thus obtained was purified by recrystallization from 75% ethanol. Their characterization data are given in **Table I**.

General procedure for the preparation of 3-propene-1,2-benzisoxazole derivatives, 5a-h

Compound **4** (0.01 M) was dissolved in dichloromethane or ether (5 mL) in another beaker silica gel (10 g) of 60-120 mesh treated with 0.02 M of sodium carbonate solution stirred and dried. This dried mixture was transferred to solution 4 and solvent was evaporated in vacuum. Resulting mixture was moistened with water (8-10 drops) stirred, covered with watch glass and kept in microwave oven (LG555F multipower oven) and irradiated for 4 min at 100% power (corresponds to 2450 MHz) with intermittent cooling. The reaction-mixture was cooled to RT and the product was extracted with dichloromethane (30 mL) and the solvent was evaporated under reduced pressure. Residue was treated with 5% NaOH in order to remove unreacted oxime **4**. The obtained compounds **5a-h** was purified by recrystallization from ethanol (**Table II**).

Table I — Physical constants and spectral data of compounds **3a-h** and **4a-h**

Compd	R	m.p. / (b.p.) °C	Yield %	^{1}H NMR (δ, ppm)
3a	4- CH_3, 5-Cl	76	90	
3b	3-Cl	56	85	
3c	3,5-dichloro	95	90	
3d	5-Br	61	85	
3e	5-Cl	57	92	
3f	3,5-dimethyl	64	95	
3g	4-CH_3	(210)	95	
3h	5-CH_3	51	87	
4a	4- CH_3, 5-Cl	151	86	1.8(s, 1H, =NOH), 2.31(d, 3H, CH_3), 6.84(s, 1H, CH_A=CH), 7.25(s, 1H, CH=CH_B), 7.36(s, 1H, Ar-H), 7.72(s, 1H, Ar-H), 11.25(s, 1H, OH)
4b	3-Cl	174-75	83	
4c	3,5-dichloro	192-94	90	1.21(s, 1H, =NOH), 2.34(d, 3H, CH_3), 6.81(s, 1H, CH_A=CH), 7.25(s, 1H, CH=CH_B), 7.31(s, 1H, Ar-H), 7.36(s, 1H, Ar-H), 12.01(s, 1H, OH)
4d	5-Br	181	85	1.66(s, 1H, =NOH), 2.31(d, 3H, CH_3), 6.85(d, 1H CH_A=CH), 7.34(q, 1H CH=CH_B), 7.46-7.55(m, 3H, Ar-H), 11.26(s, 1H, OH)
4e	5-Cl	174	92	1.62(s, 1H, =NOH), 2.32(d, 3H, CH_3), 6.85(d, 1H, CH_A=CH), 7.91-7.25(q, 1H, CH=CH_B), 7.38(m, 3H, Ar-H)
4f	3,5-dimethyl	145-47	85	
4g	4-CH_3	105	87	
4h	5-CH_3	138-40	80	

Table II — Physical constants and spectral data of compounds **5a-h**

Compd	R	m.p./(b.p.) °C	Yield %	Mol. Formula	Calcd. (Found) %			^{1}H NMR (δ, ppm)
					C	H	N	
5a	4-CH_3, 5-Cl	118	77	$C_{11}H_{10}ClNO$	63.62 (63.40)	4.85 (4.70)	6.75 (6.10)	1.57(d, 3H, CH_3), 2.35(s, 3H, CH_3), 2.51-2.75(q, 1H, =CH_B),7.26(s, 1H, CH_A=), 7.41(s, 1H, C_7-H), 7.60(s, 1H, C_4-H)
5b	3-Cl	(205)	74	$C_{10}H_8ClNO$	62.03 (62.00)	4.16 (4.00)	7.23 (7.01)	1.55(d, 3H, CH_3), 2.55-2.70(q, 1H, =CH_B),7.25(s, 1H, CH_A=),7.4-7.7(m, 3H, C_4-H, C_5-H, C_6-H)
5c	3,5-dichloro	73-75	81	$C_{10}H_7Cl_2NO$	52.66 (52.45)	3.09 (3.00)	6.14 (6.02)	1.57(d, 3H, CH_3), 2.35-2.80(q, 1H, =CH_B), 7.26(s, 1H, CH_A=), 7.51(s, 1H, C_4-H), 7.54(s, 1H, C_6-H)
5d	5-Br	(198-99)	75	$C_{10}H_8BrNO$	50.54 (50.30)	3.39 (3.20)	5.88 (5.87)	1.62(d, 3H, CH_3), 2.37-2.80(q, 1H, =CH_B), 7.26(s, 1H, CH_A=), 7.45-7.60(m, 3H, C_4-H, C_6-H, C_7-H)
5e	5-Cl	63	85	$C_{10}H_8ClNO$	62.03 (62.00)	4.16 (4.02)	7.23 (7.11)	1.61(d, 3H, CH_3), 2.34-2.77(q, 1H, =CH_B), 7.26(s, 1H, CH_A=), 7.48(d, 2H, C_6-H, C_7-H), 7.60(s, 1H, C_4-H)
5f	3,5-dimethyl	(236)	90	$C_{12}H_{13}NO$	76.98 (76.62)	7.00 (6.91)	7.48 (7.03)	2.39(d, 3H, CH_3), 2.47(s, 3H, CH_3), 2.49(s, 3H, CH_3), 2.54-2.58(q, 1H, =CH_B), 6.83(s, 1H, CH_A=), 7.06(s, 1H, C_4-H), 7.13(s, 1H, C_6-H)
5g	4-CH_3	(219)	82	$C_{11}H_{11}NO$	76.28 (76.00)	6.40 (6.00)	8.09 (7.91)	
5h	5-CH_3	(255)	79	$C_{11}H_{11}NO$	76.28 (76.21)	6.40 (6.10)	8.09 (7.95)	2.43(d, 3H, CH_3), 2.51-2.6(q, 1H, =CH_B), 7.1(s, 1H, CH_A=), 7.06(s, 1H, C_4-H), 7.28-7.41(m, 3H, C_4-H, C_6-H, C_7-H)

Table III — Antibacterial screening results of the compounds **5a-h**

Compd	Antibacterial activity (Inhibition zone in mm)			
	E. coli	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillius subtilis*
5a	-ve	-ve	-ve	-ve
5b	15	14	13	11
5c	-ve	-ve	-ve	-ve
5d	12	12	12	12
5e	12	12	14	11
5f	-ve	-ve	-ve	-ve
5g	13	15	14	13
5h	not tested	not tested	not tested	not tested
Penicillin	17	22	40	23
DMSO	-ve	-ve	-ve	-ve

-ve = no antibacterial activity

Table IV — Antifungal screening results of the compounds **5a-h**

Compd	Antifungal activity			
	Aspergillus niger	*Aspergillus flavus*	*Penicillium chrysogenum*	*Fusarium moneliforme*
5a	+ve	+ve	-ve	-ve
5b	-ve	-ve	-ve	-ve
5c	-ve	-ve	-ve	-ve
5d	-ve	-ve	-ve	-ve
5e	-ve	-ve	-ve	-ve
5f	+ve	+ve	+ve	-ve
5g	+ve	+ve	+ve	+ve
5h	not tested	not tested	not tested	not tested
Greseofulvin	-ve	-ve	-ve	-ve
Control	+ve	+ve	+ve	+ve

+ve = Growth No Antifungal activity

-ve = No growth Antifungal activity observed

Antimicrobial activity

The compounds **5a-h** were screened for their antimicrobial activity against *E. coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* by agar cup method[11,12] and for antifungal activity against *Aspergillus niger, Aspergillus flavus, Penicillium chrysogenum, Fusarium moneliforme* by poison plate method. Standard antibacterial Penicillin and antifungal Greseofulvin were also screened under similar conditions for comparison. Results are presented in **Tables III** and **IV**.

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