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SYNTHESIS OF 1-(2-HYDROXY-ARYL)-3-(5-NITRO-THIOPHEN-2-YL)-PROPENONES UNDER MICROWAVE AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

A series of 1-(2-hydroxy-aryl)-3-(5-nitro-thiophen-2-yl)-propenones were synthesized by Claisen-Schmidt condensation by 2-hydroxy acetophenes with 5-nitro-thiophene-2-carbaldehyde under both conventional and microwave irradiation methods. All the compounds were characterized by spectral data such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. The antimicrobial activities of 5-nitro-thiophene-chalcones have been assessed by evaluating the zone of inhibition required to inhibit the growth of *Escherichia coli, Klebsiella, Staphylococcus aureus* and *Basillus*.

Key words: 5-Nitro-thiophene, Chalcone, Microwave irradiation, Antimicrobial activity.

INTRODUCTION

Compounds having chalcone backbone have been found to possess various biological activities[1] such as antimicrobial[2], anti-inflammatory[3], antioxidant, anticancer[4], analgesic[5], platelet antiaggregation[6], antiulcerative[7], antimalarial[8], antiviral[9], antileishmanial[10], antitubercular[11], antihyperglycemic[12] activities. A wide range of sulfur compounds are biologically active and some of the compounds have commercial applications such as fungicides and bactericides. However, their biological activity is dependent not only on the presence of sulfur but often on the presence of additional activating groups. For example, the fungicidal activity of phenylthiocyanate is substantially enhanced by the presence of electron attracting substituent's in the aromatic ring so that the 2,4-dinitro derivative, which is highly effective against the fungus *Aspergillus niger*, has been patented as a potent antifungal agent[13]. In contrast, heterocyclic compounds such as 3-isothiazolones, are highly effective against the bacteria *Escherichia coli* and *Staphylococcus aureus* but again the relative

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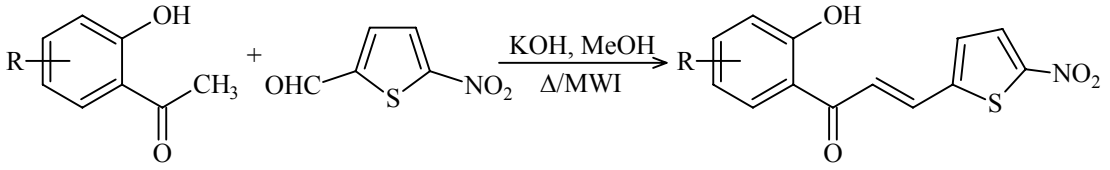
biological efficacy of these molecules is highly dependent on the nature and position of the substituent's attached to the heterocyclic ring[14]. Thus 5-chloro-*N*-methyl-3-isothiazolone is several orders of magnitude more active than the simpler *N*-methyl derivative[15].

In both cases, the biological activity of these molecules is thought to arise from their ability to initially diffuse through the membranes of bacteria or fungal cell walls and then react with important intracellular sulfur-containing proteins, or simpler thiols inside the cell, causing the cell function to be impaired. Substituted thiophenes are also biologically active[16] and like the phenylthiocyanates they generally require electron attracting nitro groups to enhance activity[17,18]. For example, 2,4-dinitrothiophene and related derivatives are fungicides[19], 2-methylamino-3,5-dinitrothiophene is an effective marine anti-fouling agent[20] and 2-acetyl-3,5-dinitrothiophene has pronounced antibiotic properties[21,22]. More recent studies have described the biocidal properties of 2,4-dinitro-5-thiomethoxythiophene and the related sulfoxide and sulfone derivatives[23], but there is little systematic information on the mode of action of the nitrothiophenes. In the present studies we have synthesised and experimentally assessed the antimicrobial activity of diverse nitrothiophene chalcones, by measuring zone of inhibition against growing cultures of the gram negative and gram positive bacterial organisms.

EXPERIMENTAL

Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Perkin-Elmer FT-IR spectrum BX. ^1H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm). Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Quatro Lc micromas (Waters Manchester.UK) (70 eV) mass spectrometer. For microwave irradiation a L.G. (M-2349 E, 2450 MHz) domestic microwave oven was used. Disc diffusion method was used to identify the antimicrobial activity on gram positive bacteria *viz. Staphylococcus aureus* and *Basillus*, and gram negative bacteria *viz. Escherichia coli* and *Klebsiella* for which Whatmann filter paper discs were used.



(1a-i) **(2)** **(3a-i)**

Scheme 1: Synthesis of 1-(2-hydroxy-aryl)-3-(5-nitro-thiophen-2-yl)-propenones (3a-i)

Table 1: Physical data of chalcones (3a-i)

Compds.	R	M.P. (^oC)	Reaction time		Yield (%)	
			Conventional (h)	MWI (min)	Conventional	MWI
3a	Hydrogen	155.157	4.0	5.0	70	89
3b	4-Methyl	158-160	3.0	4.0	75	85
3c	5-Methyl	151-153	3.0	3.0	75	90
3d	5-Chloro	166-168	4.0	5.0	64	86
3e	3,5-Dichloro	162-164	4.0	4.0	72	88
3f	4-Hydroxy	210-212	5.0	5.0	78	82
3g	5-Bromo	180-183	3.0	5.0	74	86
3h	5-Methoxy	167-169	4.0	4.0	70	90
3i	5-Nitro	186-188	3.0	3.0	74	88

Biological activity

The newly synthesized compounds (**3a-i**) were screened for their antibacterial activity against gram negative bacteria *viz. Escherichia coli* and *Klebsiella*, and gram-positive bacteria *viz. Staphylococcus aureus* and *Basillus* at concentration 50 mg/mL using ditch dilution methods. The test organism was a two hour culture of *Escherichia coli, Klebsiella, Staphylococcus aureus* and *Basillus* incubated and grown in peptone-water medium (temp-37^{o}C). DMF was used as solvent control which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37^{o}C for 24 hrs. All the compounds were found to show strong activity against gram-positive and gram negative bacteria *viz. Staphylococcus aureus*, *Basillus*, *Escherichia coli* and *Klebsiella*. These results are given in Table 2.

Table 2: Antibacterial activity of chalcones (3a-i)

Compds.	Antibacterial activity zone of inhibition (mm)			
	S. aureus	***E.coli***	***Basillus***	***Klebsiella***
3a	06	08	06	-
3b	05	07	07	-
3c	07	08	-	-

Cont…

Compds.	Antibacterial activity zone of inhibition (mm)			
	S. aureus	***E.coli***	***Basillus***	***Klebsiella***
3d	10	07	09	-
3e	13	09	13	07
3f	08	07	07	08
3g	13	08	14	06
3h	08	08	06	08
3i	06	06	07	-
Gentamycin	15	17	20	15

General procedure for the preparation of compounds (3a-i)

(a) Conventional method: To a solution of 5-nitro-thiophene-2-carbaldehyde (**2**) (1 mmol), aryl methyl ketones (**1a-i**) (1 mmol) and 20% sodium hydroxide in methanol were stirred for 3.5-4 hr at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice cold water and neutralized with dil. HCl. The resulting solid was filtered, dried and recrystallized from ethanol to obtain the compounds **(3a-i)**. The yields and M.P.s of the compounds are shown in Table 1.

(b) Microwave irradiation method: To a mixture of 5-nitro-thiophene-2-carbaldehyde (**2**) (1 mmol), aryl methyl ketones (**1a-i**) (1 mmol) and 20% sodium hydroxide in methanol were irradiated under microwave at 180 watt for 3.5-5 min. with 30 sec intervals. The reaction progress was checked by TLC. After completion of the reaction, the reaction mixture poured into ice cold water and neutralized with dil.HCl. The resulting solid was filtered, dried and recrystallized from ethanol to obtain the compounds **(3a-i)**. Details of the melting points and yields of the compounds were presented in the Table 1.

Spectral data

(3a) IR (KBr, cm^{-1}): 1645 (C=O), 1598 (C=C). ^{1}H NMR ($CDCl_3$): δ 6.91-6.92 (d, 1H, ThH), 7.02-7.04 (m, 1H, ArH), 7.40-7.41 (d, 1H, ThH), 7.48-7.51 (m, 2H, ArH), 7.63-7.67 (d, 1H, H_α), 7.73-7.77 (d, 1H, H_β), 7.89-7.90 (d, 1H, ArH), 12.78 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 113.4, 118.0, 121.4, 121.8, 123.6, 124.5, 129.0, 129.2, 137.1, 152.2, 162.1, 192.0. MS: *m/z*: 275 [M^+] (100%).

(3b) IR (KBr, cm^{-1}): 1640 (C=O), 1595 (C=C). ^1H NMR ($CDCl_3$): 2.45 (s, 3H, CH_3), 6.78-6.80 (d, 1H, ThH), 6.98-7.00 (m, 2H, ArH), 7.35-7.37 (d, 1H, ThH), 7.42-7.44 (m, 2H, ArH), 7.62-7.63 (d, 1H, ArH), 11.57 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 23.5, 114.4, 118.2, 119.8, 121.7, 124.7, 125.6, 129.8, 130.5, 137.4, 153.6, 159.6, 193.4. MS: *m/z*: 289 [M^+](100%).

(3c) IR (KBr, cm^{-1}): 1639 (C=O), 1597 (C=C).^1H NMR ($CDCl_3$): 2.46 (s, 3H, CH_3), 6.77-6.78 (d, 1H, TH), 6.98-7.00 (d, 1H, ArH), 7.34-7.35 (d, 1H, ThH), 7.41-7.42 (m, 3H, ArH), 7.60-7.61 (s, 1H, ArH), 11.51 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 23.7, 117.4, 118.4, 120.3, 121.5, 123.4, 125.0, 127.5, 128.6, 135.9, 151.8, 159.6, 192.1. MS: *m/z*: 289 [M^+](100%).

(3d) IR (KBr, cm^{-1}): 1639 (C=O), 1598 (C=C).^1H NMR ($CDCl_3$): 6.91-6.92 (d, 1H, ThH), 6.96-7.00 (d, 1H, ArH), 7.40-7.41 (d, 1H, ThH), 7.64-7.69 (m, 2H, H_α & ArH), 7.81-7.85 (d, 1H, H_β), 7.89-7.91 (s, 1H, ArH), 12.46 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 113.2, 117.6, 120.2, 120.4, 124.0, 128.9, 129.5, 137.1, 152.4, 162.2, 191.4. MS: *m/z*: 308 [M^+] (100%).

(3e) IR (KBr, cm^{-1}): 1665 (C=O), 1598 (C=C).^1H NMR ($CDCl_3$): 6.95-6.96 (d, 1H, ThH), 7.41-7.42 (d, 1H, ThH), 7.64-7.65 (s, 1H, ArH), 7.66-7.70 (d, 1H, H_α), 7.71-7.75 (d, 1H, H_β), 7.84-7.85 (s, 1H, ArH), 13.06 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 113.1, 114.1, 118.7, 119.4, 123.6, 124.5, 128.7, 129.7, 137.6, 140.8, 148.4, 153.2, 193.5. MS: *m/z*: 342 [M^+](100%).

(3f) IR (KBr, cm^{-1}): 1639 (C=O), 1599 (C=C). ^1H NMR ($CDCl_3$): 6.66-6.68 (s, 1H, ArH), 6.90-6.91 (d, 1H, ThH), 7.36-7.38 (d, 1H, ArH), 7.41-7.42 (d, 1H, TH), 7.66-7.70 (d, 1H, H_α), 7.71-7.75 (d, 1H, H_β), 7.78-7.80 (d, 1H, ArH), 12.54 (s, 1H, OH), 13.06 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 102.6, 113.6, 115.6, 119.2, 119.9, 123.6, 124.5, 125.6, 128.6, 129.4, 131.5, 136.5, 140.7, 152.6, 153.3, 193.0. MS: *m/z*: 291 [M^+](100%).

(3g) IR (KBr, cm^{-1}): 1642 (C=O), 1589 (C=C).^1H NMR ($CDCl_3$): 6.96-6.98 (d, 1H, ThH), 6.91-7.00 (d, 1H, ArH), 7.40-7.41 (d, 1H, ThH), 7.64-7.68 (m, 2H, ArH), 7.80-7.84 (d, 1H, H_β), 7.89-7.81 (s, 1H, ArH), 13.16 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 112.2, 113.4, 116.4, 118.9, 129.0, 129.1, 139.5, 152.9, 161.9, 194.3. MS: *m/z*: 354 [M^+](100%).

(3h) IR (KBr, cm^{-1}): 1644 (C=O), 1596 (C=C).^1H NMR ($CDCl_3$): 3.95 (s, 3H, OCH_3), 6.91-6.92 (d, 1H, ThH), 6.99-7.01 (d, 1H, ArH), 7.40-7.41 (d, 1H, ThH), 7.37-7.39 (d, 1H, ArH), 7.59-7.63 (d, 1H, H_α), 7.70-7.74 (d, 1H, H_β), 7.78-7.82 (s, 1H, ArH), 12.02 (s,

1H, OH). ^{13}C NMR ($CDCl_3$): 56.3, 113.1, 116.4, 119.2, 122.3, 123.6, 124.8, 125.3, 128.2, 130.5, 135.7, 152.8, 153.6, 192.4. MS: *m/z*: 305 [M^+](100%).

(3i) IR (KBr, cm^{-1}): 1645 (C=O), 1589 (C=C).^{1}H NMR ($CDCl_3$): 6.91-6.92 (d, 1H, ThH), 6.96-7.00 (d, 1H, ArH), 7.40-7.41 (d, 1H, ThH), 7.71-7.76 (m, 2H, H_α & ArH), 7.82-7.86 (d, 1H, H_β), 7.92-7.94 (s, 1H, ArH), 12.46 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 116.2, 119.7, 123.4, 126.2, 126.9, 128.4, 129.4, 137.1, 152.4, 159.4, 192.1. MS: *m/z*: 320 [M^+] (100%).

CONCLUSION

The title compounds were synthesized by conventional method and microwave irradiation method. Among these, microwave irradiation method is an easy, high yielding, convenient and green method. The process proved to be a simple and environmentally friendly technique with high rate of acceleration was achieved in performing the reaction. Synthesized compounds were tested for their antimicrobial activity. Among these, the compounds **(3e)** and **(3g)** showed maximum zone of inhibition against all organisms using Gentamycin as standard.

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