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Antimicrobial Activity and Microwave Assisted Synthesis of 1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones

Anjaiah CH*, Sunitha V, Abraham Lincoln CH, Ashok D

Department of Chemistry, Osmania University, Hyderabad-500 007, India

ABSTRACT

A series of arylsulfides have been synthesized by condensation of 1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one with arylsulfonohydrazides in the presence of Iodine under microwave irradiation methods. All the compounds tested for their in vitro antimicrobial activity against bacterial and fungal organisms and they were characterized on the basis of spectral data such as IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data and elemental analysis.

Keywords: Arylsulfides, Iodine with DMSO, Microwave irradiation, Antimicrobial activity

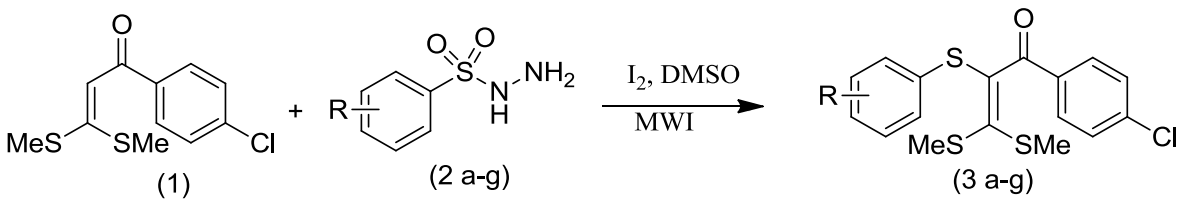
INTRODUCTION

Aryl sulfides often present in many natural products, drugs, materials science [1] and also presents in enzymes, in structural proteins of cells [2]. Many drugs having an aryl sulfide unit in their core structure are employed to treat Alzheimer's, Parkinson's, cancer, malarial, inflammatory and HIV diseases [3-6]. Among these thioethers display various biological activities such as antibacterial and analgesic activities [7-9]. The presence biological activity of aryl sulfides especially thioethers has resulted in the development of new methods to form carbon-sulfur bonds. Literature review on the synthesis of aryl sulfides shows the most synthetic procedures involve metal catalyst and the report shows the synthetic method under conventional stirring only [10]. Many of these synthetic processes suffer from one or other limitations such as drastic reaction conditions, low yields, tedious work-up procedures such as separation of metal catalyst, relatively long reaction times and co-occurrence of several side reactions. Indeed, we have been making considerable efforts for design metal free green synthetic protocols adopting a more eco-sustainable and economic approach. As a part of our research programme, we have taken up the synthesis of 1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones under microwave irradiation methods. The methods stand among the alternative routes due to various reasons like higher yields in shortest possible time and eco-friendliness [11]. However, antimicrobial agents are one of the most important weapons in the resistance of infection caused by bacterial strains. In the past few years, increase the resistance of microorganisms toward antimicrobial agents become a serious health problem so there is a need of safe, potent and novel antimicrobial agents [12]. Hence, we have screened all the synthesized compounds against various bacterial and fungal organism shows moderate results (Table 1).

MATERIALS AND METHODS

Materials

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by Thin Layer Chromatography (TLC) using precoated silica gel plates 60_{254}(Merck). Microwave reactions were carried out in milestone multi SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using Tetramethylsilane(TMS) as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was determined by using a Thermo Finnigan C, H, N, S analyzer (Scheme 1).



Scheme 1: Synthesis of 1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones (3a-g)

Table 1: Physical data of 1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones (3a-g)

Compound (R)	M.P. (°C)	Reaction time		Yield (%)	
		Conventional (h)	MWI (min)	Conventional	MWI
3a. Hydrogen	52-53	3	4	92	96
3b. 4-methyl	81-82	3	4	93	98
3c. 4-methoxy	77-79	3	4	93	98
3d. 4- chloro	67-68	3	4	91	95
3e. 4- bromo	74-75	3	4	90	95
3f. 4-hydroxy	81-83	3	4	90	95
3g. naphthyl	100-101	3	4	92	97

Antimicrobial activity

Antibacterial activity

All the compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli*and *Staphylococcus aureus* using ampicillin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 25, 50 and 100 µg/ml in Dimethyl Sulfoxide (DMSO). From the screening studies it is evident that the synthesized compounds 3d and 3e showed good antibacterial activity against all the tested organisms.

Antifungal activity

All the compounds were screened for their antifungal activity *in vitro* against *Aspergillus niger*and *Candida metapsilosis* using griseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 25, 50 and 100 µg/ml in DMSO. From the screening studies it is evident that the synthesized compounds 3b and 3f showed good antifungal activity against all the tested organisms.

Synthetic procedure for 1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones (3a-g)

Microwave irradiation method

To a mixture of 1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (1) and arylsulfonohydrazides (2a-g) was added DMSO followed by iodine. Then the reaction mixture irradiated under microwave at 160 w for 4 min with every 30 sec intervals. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with chloroform, and quenched with saturated sodium thiosulfate solution and extracted with chloroform. The compound washed with ice cold water and dried over anhydroussodium sulfate. The solvent was evaporated and the residue was subjected to column chromatography to afford pure 1-(4-chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones (3a-g).

Conventional heating method

To a mixture of 1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (1) and arylsulfonohydrazides (2a-g) was added DMSO followed by iodine. Then the reaction mixture was heated at 80°C for 3 h under solvent-free conditions. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with chloroform, and quenched with saturated sodium thiosulfate solution and extracted with chloroform. The compound was washed with ice cold water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was subjected to column chromatography to afford pure 1-(4-chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones (3a-g).

EXPERIMENTAL DATA

1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(phenylthio)prop-2-en-1-one (3a): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.33 (s, 3H), 2.63 (s, 3H), 7.27-7.32 (m, 3H), 7.42-7.43 (d, *J*=7.0 Hz, 2H), 7.47-7.49 (d, *J*=8.5 Hz, 2H), 7.80-7.82 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.6, 18.7, 128.7, 128.9, 129, 130.7, 130.9, 133.8, 134.7, 136.2, 138.1, 139.7, 189.8; MS (ESI+): *m/z*=367 $[M + H]^+$.

1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(*p*-tolylthio)prop-2-en-1-one (3b): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.17 (s, 3H), 2.24 (s, 3H), 2.49 (s, 3H), 6.94-6.95 (d, *J*=7.5 Hz, 2H), 7.15-7.17 (d, *J*=7.5 Hz, 2H), 7.33-7.35 (d, *J*=8.5 Hz, 2H), 7.67-7.69 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.5, 18.6, 21.3, 126.9, 128.8, 129.8, 130.7, 133.8, 134.3, 134.8, 139.0, 139.4, 139.6, 189.8; MS (ESI+): *m/z*=381 $[M + H]^+$..

1-(4-chlorophenyl)-2-((4-methoxyphenyl)thio)-3,3-bis(methylthio)prop-2-en-1-one (3c):^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.15 (s, 3H), 2.22 (s, 3H), 3.64 (s, 3H), 6.86-6.88 (d, *J*=7.5 Hz, 2H), 7.08-7.10 (d, *J*=7.5 Hz, 2H), 7.33-7.35 (d, *J*=8.5 Hz, 2H), 7.64-7.66 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.3, 18.4, 56.0, 119.6, 125.2, 127.4, 130.1, 132.3, 133.9, 134.4, 138.1, 138.6, 139.2, 150.9, 189.2; MS (ESI+): *m/z*=397 $[M + H]^+$..

1-(4-Chlorophenyl)-2-(4-chlorophenylthio)-3,3-bis(methylthio)prop-2-en-1-one(3d): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.19 (s, 3H), 2.49 (s, 3H), 7.12-7.14 (d, *J*=8.5 Hz, 2H), 7.20-7.22 (d, *J*=8.5 Hz, 2H), 7.36-7.37 (d, *J*=8.5 Hz, 2H), 7.68-7.69 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.4, 18.4, 128.9, 129.1, 129.7, 130.6, 134.5, 134.6, 134.8, 136.5, 137.9, 139.8, 189.5; MS (ESI+): *m/z*=402 $[M + H]^+$.

2-(4-Bromophenylthio)-1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (3e): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.38 (s, 3H), 2.68 (s, 3H), 7.32-7.38 (d, *J*=8.5 Hz, 2H), 7.46-7.48 (d, *J*=8.5 Hz, 2H), 7.55-7.56 (d, *J*=8.5 Hz, 2H), 7.87-7.89 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.6, 18.7, 122.9, 128.9, 130.5, 130.7, 132.1, 134.5, 134.6, 137.9, 138.6, 139.9, 189.6; MS (ESI+): *m/z*-444 $[M + H]^+$.

1-(4-chlorophenyl)-2-((4-hydroxyphenyl)thio)-3,3-bis(methylthio)prop-2-en-1-one (3f): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.27 (s, 3H), 2.53 (s, 3H), 6.83-7.05 (d, *J*=8.5 Hz, 2H), 7.12-7.14 (d, *J*=8.5 Hz, 2H), 7.30-7.32 (d, *J*=8.5 Hz, 2H), 7.55-7.56 (d, *J*=8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.4, 18.5, 113.4, 122.2, 129.8, 130.1, 132, 134.6, 135.1, 137.2, 137.5, 139.3, 151.6, 188.9; MS (ESI+): *m/z*=382 $[M + H]^+$.

1-(4-Chlorophenyl)-3,3-bis(methylthio)-2-(naphthalen-2-ylthio)prop-2-en-1-one (3g): ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.22 (s, 3H), 2.51 (s, 3H), 7.31-7.33 (d, *J*=8.5 2H), 7.38-7.39 (dd, *J*=1.0, 8.0 Hz, 1H), 7.44-7.45 (m, 2H), 7.65-7.70 (dd, *J*=8.5, 15.0 Hz, 4H), 7.74-7.75 (d, *J*=5.0 Hz, 1H), 7.80 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ=16.7, 18.7, 126.6, 126.9, 127.7, 128.4, 128.6, 128.8, 130.1, 130.8, 132.8, 133.4, 134.7, 137.3,

137.5, 139.6, 189.8; MS (ESI+): *m/z*=417 $[M + H]^+$

CONCLUSION

We synthesize 1-(4-chlorophenyl)-3,3-bis(methylthio)-2-(arylthio)prop-2-en-1-ones under microwave irradiation and conventional heating method, the microwave irradiation method proved to be eco-friendly, with shatter reaction time and higher yield compared to that of conventional method. In the microbial activity the compounds **3d** and **3e** shows good activities against all bacterial organisms, the compounds **3b** and **3f** shows good activities against all fungal organisms.

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