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MICROWAVE ASSISTED SYNTHESIS OF 6-BENZOYL-5-METHYL-2-[(*Z*)-1-ARYL METHYLIDENE]-2,3-DIHYDROFURO [3',2' :4,5] BENZO[b] FURAN-3-ONES AND THEIR ANTIBACTERIAL ACTIVITY

Ashok D*, Sudershan K[1] and Khalilullah M[2]

**Department of chemistry, Osmania University, Hyderabad -500 007, India,*
[1]Sven Genetech Ltd, I.D.A. Phase-II, Cherlapally, Hyderabad-500 051, India
[2]Department of Chemistry, JNTU, Kupkatpally, Hyderabd-500 072, India
Email: ashokdou@gmail.com

Abstract:
A series of 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro[3',2':4,5] benzo[b]furan-3-ones have been prepared by an efficient oxidation of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones with cupric bromide or mercuric acetate under microwave irradiation. The structures of newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. All the compounds were screened for their antibacterial activity.

Key Words: Furanoaurones, benzofuran, cupric bromide, mercuric acetate, microwave irradiation, antibacterial activity.

Introduction

A number of benzofuran derivatives are known to possess anti-inflammatory[1,2], anticancer[3,4], antibacterial[5], antifungal[6], antiallergic[7], antihistaminic[8], estrogenic and anti-implantation[9,10] properties. Aurones have been reported to exhibit various pharmacological activities[11] such as antifungal, antibacterial, antiviral, antileishmenial activities[12-14]. In order to know the combined effect of both benzofuran and aurone moieties on biological activities, herein we report the synthesis of 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro[3',2':4,5]benzo[b]furan-3-ones (furanoaurones) **(3a-f)** by an efficient oxidation of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones with cupric bromide or mercuric acetate. The use of microwave irradiation in organic synthesis has become increasingly popular as an environmental benign technology. Microwave assisted synthesis[15,16] leads to significantly reduced reaction times, enhanced yields and environment friendly. Therefore in the present study we have synthesized the title compounds under microwave irradiation.

Results and Discussion

The required starting materials, (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones[17] were synthesized by condensing 5-Acetyl-2-benzoyl-6-hydroxy-3-methyl

benzofuran[18] with aromatic/hetero aromatic aldehydes in the presence of sodium methoxide under solvent-free microwave irradiation. The title compounds 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro[3',2':4,5]benzo[b]furan-3-ones **(3a-f)** were synthesized in good yields by oxidizing (E)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones with cupric bromide in dimethyl sulphoxide or mercuric acetate in pyridine, under microwave irradiation. The synthesis of **3a-f** was also carried out under conventional heating. The physical data of compounds **3a-f** are given in **Table-1**. The geometry of the exocyclic double bond of aurone was confirmed by diagnostic ^{13}C-NMR signal[19] at δ 111.8.

Scheme:

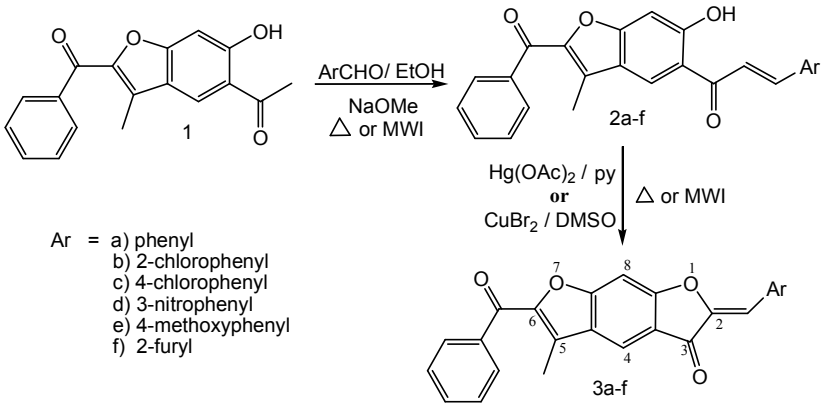

Table-1: Physical data of 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro [3',2':4,5]benzo [b]furan-3-ones(3a-f)

Compound	M.P (°C)	M.F. (M.Wt.)	Conventional heating				Microwave irradiation			
			$CuBr_2$		$Hg(OAc)_2$		$CuBr_2$		$Hg(OAc)_2$	
			Time (hr)	Yield (%)	Time (hr)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	20	$C_{25}H_{16}O_4$ (380)	1	61	1	68	2	70	1.5	88
3b	237	$C_{25}H_{15}O_4Cl$ (414)	1.5	57	1	63	3	68	1.5	81
3c	260	$C_{25}H_{15}O_4Cl$ (414)	1	56	1	65	2	64	1.5	84
3d	245	$C_{25}H_{15}O_6N$ (425)	1.5	54	2	63	3	69	2	78
3e	242	$C_{26}H_{18}O_5$ (410)	1.5	58	1	65	2	71	2	90
3f	>290	$C_{23}H_{14}O_5$ (370)	1.5	54	1	61	3	73	1.5	84

Antibacterial Activity

The activity was determined using cup-plate agar diffusion method[20] by measuring the inhibition zone in mm. All the compounds were screened for their antibacterial activity against a variety of bacterial strains such as Bacillus subtilis (ATCC-6633), Staphylococcus aureus (ATCC-29737), Escherichia coli (ATCC-10536), and Pseudomonas aeruginosa (ATCC-27853) using Streptomycin, Tetracycline, Chloramphenicol, Carbenicillin as standard drugs. Nutrient agar was used as a culture medium. A 1mg/ml solution in dimethylformamide was used. DMF showed no inhibition zones. The agar medium was inoculated with bacterial cultures tested. After 24 hours of incubation at 37^{o}C, the diameter of inhibition zone (mm) was measured. The results of the antibacterial activity are given in **Table-2.** Among the compounds screened, 3c, 3d, 3e exhibited good antibacterial activity.

Table-2: Antibacterial activity of 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro [3',2':4,5]benzo[b]furan-3-ones **(3a-f)** and inhibition zones.

Compound No.	Gram Positive Bacteria		Gram Negative Bacteria	
	Bacillus subtilis (ATCC-6633)	Staphylococcus aureus (ATCC-29737)	Escherichia coli (ATCC-10536)	Pseudomonas aeruginosa (ATCC-27853)
3a	16 mm	16 mm	17 mm	8mm
3b	15 mm	16 mm	16 mm	8mm
3c	17 mm	17 mm	21 mm	11 mm
3d	17 mm	19 mm	20 mm	9 mm
3e	18 mm	19 mm	22 mm	9 mm
3f	15 mm	15 mm	16 mm	9mm
Standard	22 mm Streptomycin	15 mm Tetracycline	13 mm Chloramphenicol	13 mm (Carbenicillin)

Experimental

Melting points were determined on Polmon MT 96 melting point apparatus and are uncorrected. IR Spectra were measured as KBR pellets on shimadzu FTIR-8400S ^{1}H-NMR Spectra and ^{13}C-NMR spectra were recorded in DMSO-d_6 on Avance 300 spectrometer using tetramethyl silane as an internal standard. Elemental analysis was determined on Thermo Finnigan CHNS analyzer. Mass spectra were recorded on LCMS-2010A Shimadzu spectrophotometer. The purity of the compounds was checked by TLC using precoated silica gel plates (F-254), Merck. Microwave irradiations were carried out in Multisynth series microwave system.

General procedure for the synthesis of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo [b]furan-5-yl)-3-aryl-2-propen-1-ones (2a-f)

Thoroughly mixed mixture of **1** (0.001 mol), appropriate aromatic/hetero aromatic aldehydes (0.001mol) and sodium methoxide (0.004 mol) was taken in a quartz tube and inserted into teflon vial with screw capped and then subjected to microwave irradiation at the constant temperature 70°C for 5-6 min. After the completion of reaction as an indicated by TLC, the reaction mixture was poured on to crushed ice and acidified with dil. HCl. The solid separated was filtered and recrystallized from methanol as yellow powder.

Synthesis of 6-Benzoyl-5-methyl-2-[(*Z*)-1-arylmethylidene]-2,3-dihydrofuro[3',2':4,5] benzo [b]furan-3-ones (3a-f).

Conventional method

A mixture of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones **(2a-f)** (0.001 mol) and cupric bromide (0.001 mol) in DMSO (5ml) or mercuric acetate (0.0015 mol) in pyridine (5ml) was refluxed for appropriate time (Table-1). The progress of the reaction was monitored with TLC. The reaction mixture was diluted with chilled water and acidified with dil. HCl. The solid separated was filtered and recrystallized from methanol as pale yellow powder.

Microwave irradiation method

A mixture of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-3-aryl-2-propen-1-ones **(2a-f)** (0.001 mol) and cupric bromide (0.001 mol) in DMSO (5ml) or mercuric acetate (0.0015 mol) in pyridine (5 ml) was taken in a quartz tube and inserted into teflon vial with screw capped and then subjected to microwave irradiation at the constant temperature 100°C for appropriate time (Table-1). After the completion of reaction as indicated by TLC, the reaction mixture was diluted with chilled water and acidified with dil. HCl. The solid separated was filtered and recrystallized from methanol as pale yellow powder.

6-Benzoyl-5-methyl-2-[(*Z*)-1-phenylmethylidene]-2,3-dihydrofuro[3',2':4,5]benzo[b] furan-3-one (3a).

IR (KBr, cm^{-1})**:**1718(furanone C=O), 1648 (C=C), 1612(benzoyl C=O)[17, 18]. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.66(s, 3H, CH_3), 6.89 (s, 1H, benzylidene-H), 6.93 (s, 1H, C_8-H), 7.45-7.71(m, 5H, phenyl), 7.95-8.03 (m, 3H, $C_{3,\ 4,\ 5}$-H of benzoyl), 8.09-8.15 (m, 2H, $C_{2,\ 6}$-H of benzoyl), 8.29(s, 1H, C_4-H); MS: m/z = 381$[M+H]^+$, Anal. Calcd. for $C_{25}H_{16}O_4$ C, 78.9; H, 4.21%. Found: C, 78.7; H, 4.21%.

6-Benzoyl-5-methyl-2-[(*Z*)-1-o-chlorophenyl methylidene]-2,3-dihydrofuro [3',2':4,5] benzo [b]furan-3-one (3b).

IR (KBr, cm^{-1})**:**1713(furanone C=O), 1649(C=C), 1618(benzoyl C=O).^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H, CH_3), 7.05(s, 1H, benzylidene-H), 7.06 (s, 1H, C_8-H), 7.44-7.73 (m, 4H, Ar-H), 7.86-7.96 (m, 3H, $C_{3,\ 4,\ 5}$-H of benzoyl), 8.07-8.13 (d, 2H, $C_{2,\ 6}$-H of benzoyl), 8.42 (s,1H, C_4-H); MS: m/z = 415$[M+H]^+$, Anal. Calcd. for $C_{25}H_{15}O_4Cl$; C, 72.4; H, 3.62%. Found: C, 72.4; H, 3.72%.

6-Benzoyl-5-methyl-2-[(*Z*)-1-p-chlorophenylmethylidene]-2,3-dihydrofuro[3',2':4,5] benzo [b]furan-3-one (3c).

IR (KBr, cm^{-1})**:**1710(furanone C=O), 1647(C=C), 1622(benzoyl C=O). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H, CH_3), 6.89(s, 1H, benzylidene-H), 6.93 (s, 1H, C_8-H), 7.48-7.72 (m, 4H, Ar-H), 7.93-8.01 (m, 3H, $C_{3,4,5}$-H of benzoyl), 8.05-8.08 (m, 2H, $C_{2,6}$-H of benzoyl), 8.27(s, 1H, C_4-H); MS: m/z = 415$[M+H]^+$, Anal. Calcd. for $C_{25}H_{15}O_4Cl$; C, 72.4; H, 3.62%. Found: C, 72.52; H, 3.66%.

6-Benzoyl-5-methyl-2-[(*Z*)-1-m-nitro phenyl methylidene]-2,3-dihydrofuro [3',2':4,5] benzo [b]furan-3-one (3d).

IR (KBr, cm^{-1}):1715(furanone C=O), 1644(C=C), 1619(benzoyl C=O). ^{1}H- NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3H, CH_3), 7.08(s, 1H, benzylidene-H), 7.13 (s, 1H, C_8-H), 7.54-7.84 (m, 2H, C-$_{5,6}$-H, Ar-H), 7.90-8.14 (m, 3H, C $_{3,4,5}$-H of benzoyl), 8.31(s, 1H, C_4-H), 8.38-8.43 (m, 2H, $C_{2,6}$-H of benzoyl) 8.64-8.82 (m, 2H, C $_{2',4'}$ -H Ar-H); MS: m/z = 426$[M+H]^+$, Anal. Calcd. for $C_{25}H_{15}O_6N$: C, 70.5; H, 3.52; N, 3.29%, Found: C, 70.52; H, 3.66; N, 3.33%.

6-Benzoyl-5-methyl-2-[(*Z*)-1-p-methoxyphenyl methylidene]-2,3-dihydrofuro [3',2': 4,5] benzo [b]furan-3-one (3e).

IR (KBr, cm^{-1}):1701(furanone C=O), 1646(C=C), 1618(benzoyl C=O). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.57 (s, 3H, CH_3), 3.84(s, 3H, OCH_3), 6.90(s, 1H, benzylidene-H), 7.03-7.08 (d, 2H, C $_{2',6'}$ -H Ar-H), 7.56-7.76 (m, 4H $C_{3,4,5}$-H of benzoyl and C_8-H), 8.08-8.15(d, 4H, C $_{2,6}$-H of benzoyl, and $C_{3',5'}$ -H Ar-H), 8.29(s, 1H, C_4-H); ^{13}C-NMR (75MHz, DMSO-d_6): δ 9.9, 55.38, 111.8, 114.5, 118.2, 124.4, 128.0, 128.5, 129.5, 133.0, 133.6, 137.0, 145.6, 148.2, 160.7, 184.1; MS: m/z = 411$[M+H]^+$, Anal. Calcd. for $C_{26}H_{18}O_5$: C, 76.09; H%, 4.39. Found: C, 76.04; H, 4.48%.

6-Benzoyl-5-methyl-2-[(*Z*)-1-2-furyl phenyl methylidene]-2,3-dihydrofuro [3',2':4,5] benzo [b]furan-3-one (3f).

IR (KBr, cm^{-1}):1701(furanone C=O), 1642(C=C), 1617(benzoyl C=O). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.55 (S, 3H, CH_3), 6.83(s,1H, benzylidene-H), 6.89 (s, 1H, H-8), 7.54-7.75 (m, 3H, furyl), 7.94-8.03 (m, 3H, $C_{3,4,5}$-H of benzoyl), 8.08-8.15(d, 2H, $C_{2,6}$-H of benzoyl), 8.27(s, 1H, C_4-H); MS: m/z = 370$[M]^+$, Anal. Calcd. for $C_{23}H_{14}O_5$; C, 74.59; H, 3.78%. Found: C, 74.64; H, 3.87%.

Conclusion

In Conclusion, we have successfully synthesized new furanoaurones under microwave irradiation. This methodology provides an efficient, time saving and environmentally benign synthesis. The reaction time is dramatically reduced to 1.5-3.0 min. Also, solvent-free synthesis of chalcones (2a-f) is non polluting green approach.

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