Indian Journal of Chemistry
Vol. 44B, May 2005, pp 1079-1083

Synthesis of 1-(6-methylbenzofuran-2-yl)-3-aryl/[4-(β-substitutedethoxy)phenyl]propenones as marked anti-microbial agents

Y Thirupathi Reddy* & P Narsimha Reddy

Department of Chemistry, National Institute of Technology, Warangal 506004 (AP)

and

Md Abdul Mannan, B Sunil kumar & T Gururaj

Dept. of Pharmacy, V. L. College of Pharmacy, Raichur 584101, India.

Email: ytirupatireddy@yahoo.com

Received 19 November 2003; accepted (revised) 3 March 2004

2-Acetyl-6-methylbenzofuran **1** has been synthesized under PTC conditions and conventional method (acetone/K_2CO_3). 1-(6-Methylbenzofuran-2-yl)-3-arylpropenones **3a-e** and 1-(6-methylbenzofuran-2-yl)-3-[4-(β-substitutedethoxy) phenyl]-propenones **4a-e** have also been synthesized. The compounds **3a-e** and **4a-d** have been screened for antibacterial and antifungal activities.

IPC: **Int.Cl.[7] C 07 D // A 61 P31/04, 31/10**

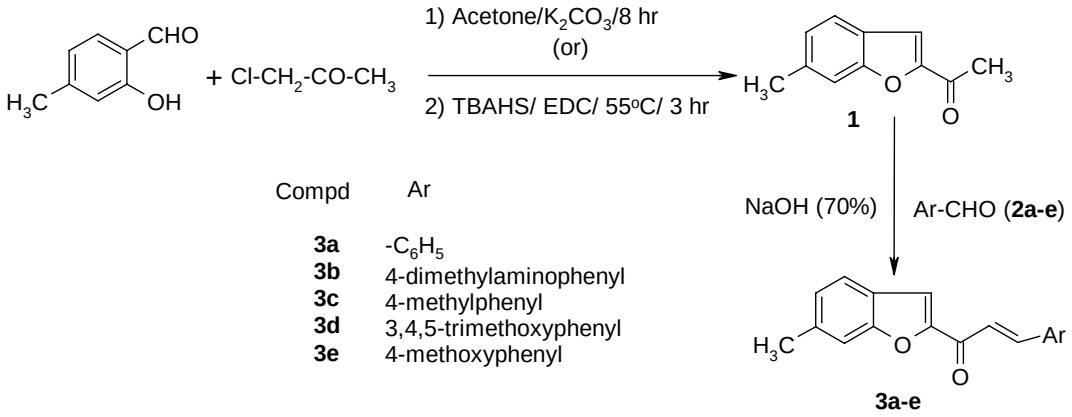
Benzofurans[1-5], 2-furylbenzofurans[6], benzofuran-2-ones[7], benzodifurans[8] and benzofuran analogues of chalcones[9-12] and basic ethers of benzodifurans[13] are gaining importance in recent years as anti-microbial, spasmolytic, anti-implantation and anti-inflammatory agents[14,15]. Our studies on cyclised triaryl ethelene systems as anticancer agents[16-18] have been reported. This observation prompted us to undertake the synthesis of 1-(6-methylbenzofuran-2-yl)-3-arylpropenones **3a-e** and 1-(6-methylbenzofuran-2-yl)-3-[4-(β-substitutedethoxy)phenyl]propenones **4a-e**.

Results and Discussion

The synthesis of 2-acetylbenzofuran **1** was reported by earlier workers in 70% yield within 7-8 hr by conventional method using dry acetone/baked K_2CO_3. In order to improve the yield and reduce the reaction time, we have developed the procedure for the synthesis of 2-acetylbenzofuran **1**, which is formed within 2-3 hr in 92% yield under PTC conditions by using $TBAHSO_4$ (tetrabutyl ammonium hydrogen sulphate) as catalyst. The 1-(6-methylbenzofuran-2-yl)-3-arylpropenones **3a-e** were synthesized from the reaction of **1** and aromatic aldehydes **2a-e** in the presence of 70% NaOH in ethanol at room temperature. The **3e** was demethylated in pyridine hydrochloride to get 1-(6-methylbenzofuran-2-yl)-3-(4-hydroxyphenyl)propenone **4a**. The compound **4a** when treated with β-*t*-alkylaminochlorohydrochlorides in anhydrous K_2CO_3 and dry acetone gave 1-(6-methylbenzofuran-2-yl)-3-[4-(β-substitutedethoxy)phenyl]propenones **4b-e**. The reaction sequence is depicted in **Scheme Ia** and **Scheme Ib**.

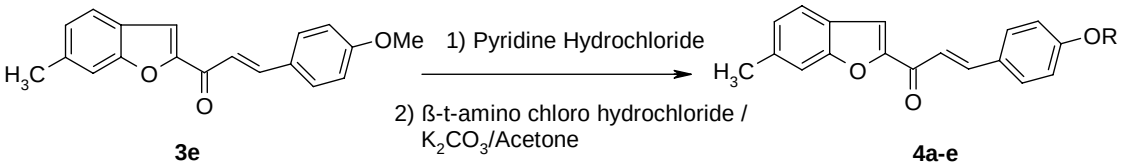
It is also observed that excellent yields of 1-(6-methylbenzofuran-2-yl)-3-arylpropenones were obtained when simple and substituted benzaldehydes were treated with compound **1**. The yields of the compounds **3b** and **3d** slightly decreased when 4-N,N-dimethylaminobenzaldehyde and 4-methoxybenzaldehydes were used.

The compounds **3a-e** and **4a-e** were characterized by UV, IR, ^{1}H NMR and mass spectral data. The UV spectra of **3a-e** and **4a-e** displayed two absorption bands in the regions 295-302 and 315-328 nm as compared to the unsubstituted benzofuran[20], which showed three absorption bands at 245, 275 and 282 nm. It is evident that all the bands in **3a-e** and **4a-e** are observed at longer wavelength regions. This bathochromic shift is due to the presence of cinnamoyl group, which facilitates the extended conjugation. The



Compd	Ar
3a	-C_6H_5
3b	4-dimethylaminophenyl
3c	4-methylphenyl
3d	3,4,5-trimethoxyphenyl
3e	4-methoxyphenyl

Scheme Ia



Compd	R
4a	H
4b	-CH_2-CH_2-N(Et)$_2$
4c	-CH_2CH_2—N O
4d	-CH_2CH_2—N
4e	-CH_2CH_2—N

Scheme Ib

IR spectra of **3a-e** and **4a-e** showed three bands in the region 1650-1680 (-CO- str.), 1595-1630 (-CH=CH- str., belongs to cinnamoyl group) and 1240-1260 cm^{-1} (-C-O-C- str., furan ring). The ^{1}H NMR (DMSO-d_6) spectra of compounds **3a-e** and **4a-e** were found to be in good agreement with 1-(6-methylbenzofuran-2-yl)-3-arylpropenones.

Antimicrobial activity

The compounds **3a-e** and **4a-d** were screened *in vitro* against pathogenic bacteria *Bacillus subtilis, Escherichia coli, Staphylococcus aureus* and *Proteus vulgaris* at 10 µg/mL and 20 µg/mL in DMF using cup-plate agar diffusion method[21]. The zone of inhibition was measured in cm. The compounds **3c**, **3d**, **3e**, **4c** and **4d** were highly active against *B. substilis*, compounds **3b**, **3d**, **4c** and **4d** were highly active against *E. coli* and compounds **3d**, **3e**, **4c** and **4d** were highly active against *P. vulgaris*. The remaining compounds were moderately active against all organisms. The antibacterial activity was compared with the known antibiotic *Ampicillin* and the results are given in **Table I**.

The compounds **3a-e** and **4a-e** were also screened for their antifungal activity against *Candida albicans* at 120 µg/mL, 360 µg/mL, 600 µg/mL and 840 µg/mL concentrations using the glass slide humid chamber technique[22]. The compounds **3a**, **3d** and **4d** are highly active against *C. albicans*. The remaining compounds showed moderate activity against *C. albicans*. The antifungal activity was compared with known antibiotic *Flucanazole* and the results are presented in **Table II**.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The UV spectra were recorded on a Shimadzu UV-160A UV-Vis-NIR spectro-

Table I — Antibacterial activity of **3a-e** and **4a-d**
Zone of inhibition (cm)

Compd	Concentration μg/mL	*E.coli*	*P. vulgaris*	*B. subtilis*
3a	10	1.2	1.1	0.9
	20	1.5	1.4	1.3
3b	10	1.5	0.9	1.1
	20	1.7	1.3	0.9
3c	10	1.2	1.0	1.3
	20	1.4	1.4	1.7
3d	10	1.4	1.3	1.4
	20	1.7	1.6	1.7
3e	10	1.1	1.4	1.4
	20	1.4	1.6	1.6
4a	10	1.2	0.8	0.9
	20	1.5	1.2	1.4
4b	10	1.2	1.0	1.1
	20	1.5	1.4	1.4
4c	10	1.5	1.2	1.3
	20	1.8	1.8	1.7
4d	10	1.3	1.2	1.2
	20	1.7	1.7	1.6
Ampicillin	10	1.4	1.5	1.5
	20	1.8	1.7	1.8

Table II — % of Spore germination at different concentrations against *Candida albicans*

Compd	Concentration			
	120 μg/mL	360 μg/mL	600 μg/mL	840 μg/mL
3a	79	84	87	90
3b	76	78	82	85
3c	72	77	80	83
3d	78	84	86	93
3e	75	78	80	84
4a	71	78	79	87
4b	77	79	81	85
4c	68	74	82	86
4d	82	86	87	95
4e	74	77	79	83
Flucanazole	84	87	95	98

photometer; IR spectra on a Shimadzu FTIR model 8010 spectrophotometer; ^{1}H NMR spectra in DMSO-d_6 on a Varian C_{17}-20-ZM-390-20 MHz spectrophotometer using TMS as an internal standard; and mass spectra on EIMS at 70eV. The C, H, N and O analyses of compounds were done on a Carlo Erba model EA1108 CHNS-O elemental analyzer.

Synthesis of 2-acetyl-6-methylbenzofuran 1 under PTC conditions. To a magnetically stirred solution of 2-hydroxy-4-methylbenzaldehyde (0.01 mole, 1.36 g) in EDC (30 mL), 20% K_2CO_3 (30 mL) and $TBAHSO_4$ (100 mg) were added. The reaction mixture was heated to 55° and chloroacetone (0.01 mole) in EDC (10 mL) was added dropwise over a period of 30 min at 55-60° and stirred for 3 hr. The organic layer was separated and washed with 5% NaOH solution and then with water. The resulting organic layer was dried over anhydrous Na_2SO_4. The excess solvent was removed under reduced pressure and the crude product was recrystallized from aqueous dioxan.

Synthesis of 2-acetyl-6-methylbenzofuran 1 by conventional method (dry acetone /baked K_2CO_3). To a magnetically stirred solution of 2-hydroxy-4-methylbenzaldehyde (0.1 mole, 13.6g) in dry acetone (100 mL) and baked K_2CO_3 (20g), was added with chloroacetone (9.2 mL, 0.1 mole) in EDC (100 mL) in 30 min. The reaction mixture was refluxed for 8 hr on a water-bath. It was filtered and washed thoroughly with acetone. The resulting organic layer was dried over anhydrous Na_2SO_4. The excess solvent was removed under reduced pressure and the crude product was recrystallized from aqueous dioxan.

Synthesis of 1-(6-methylbenzofuran-2-yl)-3-aryl-propenones 3a-e. To a magnetic stirred solution of **1** (0.01 mole, 1.74g) and aromatic aldehydes (0.01 mole) in ethanol (20 mL), 70% NaOH solution (5 mL) was added slowly at 5-10°. The reaction mixture was further stirred for 2 hr and left overnight at room temperature. The mixture was acidified using dilute hydrochloric acid to get deep coloured (yellow-orange) solids. The solid separated was collected by filtration and purified by crystallization from dioxan.

Synthesis of 3-(4-hydroxyphenyl)-1-(6-methyl-benzofuran-2-yl)propenone 4a. Compound **3e** (0.01 mole, 2.78g) and freshly distilled pyridine hydrochloride (0.01 mole, 11.5g) were heated at 200°C for 30 min. The reaction mixture was cooled, decomposed with water, filtered and the crude product obtained was recrystallised from aqueous dioxan.

Synthesis of 1-(6-methylbenzofuran-2-yl)-3-[4-(β-diethylaminoethoxy)phenyl] propenone 4b. A mixture of compound **4a** (0.01 mole, 3.92g), diethylaminoethyl chloro hydrochloride (0.01 mole, 1.72g) in anhydrous K_2CO_3 (5g) and dry acetone (300 mL) was refluxed for 20 hr. The reaction mixture was filtered and concentrated to yield **4b**, which was recrystallized from aqueous dioxan.

Compounds **4b-e** were synthesized similarly.

1-(6-Methylbenzofuran-2-yl)-3-phenylpropenones 3a: mp 140°, yield 83%; UV (MeOH): 302 and 320 nm; IR (cm^{-1}): 1670, 1630 and 1245; MS m/z (%): M^+, 262 (8), 131 (100), 118 (12); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, C_6-CH_3), 6.6 (d, 2H, -CO-CH=CH-), 7.1-7.5 (m, 9H, Ar-H); Anal. Calcd for $C_{18}H_{14}O_2$ (262): C, 82.42; H, 5.38. Found: C, 82.43; H, 5.37%.

3-(4-N,N-Dimethylaminophenyl)-1-(6-methylbenzofuran-2-yl)propenone 3b: mp 159°, yield 71%; UV (MeOH): 300 and 315 nm; IR (cm^{-1}): 1665, 1620 and 1235; MS m/z (%): M^+, 305 (6); ^1H NMR (DMSO-d_6): δ 2.5 (s, 3H, C_6-CH_3), 3.1 (s, 6H, -$N(CH_3)_2$), 6.7 (d, 2H, -CO-CH=CH-), 6.9-7.1 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.8 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{20}H_{19}NO_2$ (305): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.69; H, 6.26; N, 4.57%.

3-(4-Methylphenyl)-1-(6-methylbenzofuran-2-yl)-propenone 3c: mp 165°, yield 80%; UV (MeOH): 302 and 318 nm; IR (cm^{-1}): 1676, 1630 and 1255; MS m/z (%): M^+, 276 (8); ^1H NMR (DMSO-d_6): δ 2.5 (s, 6H, C_6-CH_3 and $C_{4'}$-CH_3), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.1-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{19}H_{16}O_2$ (276): C, 82.58; H, 5.84. Found: C, 82.57; H, 5.85%.

3-(3,4,5-Trimethoxyphenyl)-1-(6-methylbenzofuran-2-yl)propenone 3d: mp 148°, yield 70%; UV (MeOH): 305 and 322 nm; IR (cm^{-1}): 1680, 1624 and 1245; MS m/z (%): M^+, 352 (7); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, C_6-CH_3), 3.8 (s, 9H, $C_{3'}$, $C_{4'}$, $C_{5'}$-OCH_3), 6.5 (d, 2H, -CO-CH=CH), 7.1-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{21}H_{20}O_5$ (352): C, 71.58; H, 5.72. Found: C, 71.60; H, 5.70%.

3-(4-Methoxyphenyl)-1-(6-methylbenzofuran-2-yl)propenone 3e: mp 138°, yield 79%; UV (MeOH): 303 and 315 nm; IR (cm^{-1}): 1678, 1630 and 1250; MS m/z (%): M^+, 292 (5); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, C_6-CH_3), 3.1 (s, 3H, $C_{4'}$-OCH_3), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{19}H_{16}O_3$ (292): C, 78.06; H, 5.52. Found: C, 78.02; H, 5.56%.

3-(4-Hydroxyphenyl)-1-(6-methylbenzofuran-2-yl)propenone 4a: mp 192°, yield 78%; UV (MeOH): 303 and 322 nm; IR (cm^{-1}): 3300, 1675, 1628 and 1245; MS m/z (%): M^+, 278 (6), 262 (4), 131 (100), 118 (15); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, C_6-CH_3), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz), 10.5 (s, 1H, 4′-OH, D_2O exchangeable); Anal. Calcd for $C_{18}H_{14}O_3$ (278): C, 77.68; H, 5.07. Found: C, 77.65; H, 5.10%.

1-(6-Methylbenzofuran-2-yl)-3-[4-(β-diethylaminoethoxy)phenyl]propenone 4b: mp 228°, yield 75%; UV (MeOH): 305 and 328 nm; IR (cm^{-1}): 1665, 1625 and 1255; MS m/z (%): M^+, 377 (8); ^1H NMR (DMSO-d_6): δ 1.02 (t, 6H, -$N(CH_3)_2$, *J*=7.5Hz), 2.4 (s, 3H, 6-CH_3), 2.55-2.6 (m, 4H, -$N(CH_2)_2$), 2.77 (t, 2H, -CH_2-N, *J*=6Hz), 3.94 (t, 2H, -OCH_2, *J*=6Hz), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{24}H_{27}NO_3$ (377): C, 76.36; H, 7.21; N, 3.71. Found: C, 76.35; H, 7.20; N, 3.73%.

1-(6-Methylbenzofuran-2-yl)-3-[4-(β-morpholinoethoxy)phenyl]propenone 4c: mp 212°, yield 73%; UV (MeOH): 303 and 320 nm; IR (cm^{-1}): 1675, 1630 and 1245; MS m/z (%): M^+, 391 (7); ^1H NMR (DMSO-d_6): δ 2.4 (s, 3H, C_6-CH_3), 2.56-3.0 (m, 4H, -$N(CH_2)_2$), 3.0 (t, 2H, -CH_2-N, *J*=6Hz), 4.0 (t, 2H, -OCH_2, *J*=6Hz), 4.2 (m, 4H, -$O(CH_2)_2$), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{24}H_{25}NO_4$ (391): C, 73.64; H, 6.44; N, 3.58. Found: C, 73.65; H, 3.56; N, 3.74%.

1-(6-Methylbenzofuran-2-yl)-3-[4-(β-piperidinoethoxy)phenyl]propenone 4d: mp 218°, yield 68%; UV (MeOH): 308 and 323 nm; IR (cm^{-1}): 1665, 1624 and 1232; MS m/z (%): M^+, 389 (9); ^1H NMR (DMSO-d_6): δ 1.62 (m, 6H, $C_{3''}$-H, $C_{4''}$-H, $C_{5''}$-H), 2.4 (s, 3H, C_6-CH_3), 2.55-2.6 (m, 4H, $C_{2''}$-H, $C_{6''}$-H), 2.9 (t, 2H, -CH_2-N, *J*=6Hz), 4.1 (t, 2H, -OCH_2, *J*=6Hz), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3''}$-H, $C_{5''}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d, 2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{25}H_{27}NO_3$ (389): C, 77.09; H, 6.99; N, 3.60. Found: C, 77.05; H, 6.98; N, 3.65%.

1-(6-Methylbenzofuran-2-yl)-3-[4-(β-pyrrolidinoethoxy)phenyl]propenone 4e: mp 202°, yield 73%; UV (MeOH): 309 and 325 nm; IR (cm^{-1}): 1668, 1626 and 1230; MS m/z (%): M^+, 375 (8); ^1H NMR (DMSO-d_6): δ 1.69 (m, 4H, $C_{3''}$-H, $C_{4''}$-H), 2.4 (s, 3H, C_6-CH_3), 2.6 (m, 4H, $C_{2''}$-H, $C_{5''}$-H), 2.9 (t, 2H, -CH_2-N, *J*=6Hz), 4.1 (t, 2H, -OCH_2, *J*=6Hz), 6.6 (d, 2H, -CO-CH=CH-), 6.9-7.0 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, *J*=9Hz), 7.2-7.9 (m, 4H, C_3-H, C_4-H, C_5-H, C_7-H), 8.0-8.1 (d,

2H, $C_{2'}$-H, $C_{6'}$-H, *J*=9Hz); Anal. Calcd for $C_{24}H_{25}NO_3$ (375): C, 76.77; H, 6.71; N, 3.73. Found: C, 76.75; H, 6.72; N, 3.74%.

Acknowledgement

The authors are thankful to AICTE for financial assistance and to the Director, IICT for ^{1}H NMR and mass spectral analysis.

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