

Note

Synthesis of benzo[b]furan Mannich bases under solventless, PTSA/PTC catalytic conditions assisted by microwave irradiation

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Condensation of 2-aroyle-6-hydroxy-3-methyl-5-acetyl-benzo[b]furan with different amines and paraformaldehyde in the presence of *p*-toluene sulfonic acid (PTSA) or PTC [tetra butyl ammonium sulphate] leads to the synthesis of benzo[b]furan Mannich bases by a solventless PTSA/PTC catalytic reaction under microwave irradiation.

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A large number of benzofurans have been associated with various biological activities^{1,2}. Benzofuran derivatives are used as cosmetics² and pharmaceuticals³. Mannich bases are versatile synthetic building blocks which can be easily converted into valuable organic derivatives and have many attractive applications in paint, polymer chemistry and pharmaceutical products⁵. Now a days the use of Mannich bases in cancer therapy is one of the several current areas of research⁶. The Mannich reaction is a three-component condensation reaction consisting of active hydrogen containing compound, formaldehyde and an amine.

In the last few years⁷, there has been a growing interest in the use of microwave heating in organic synthesis. The use of such microwave reaction conditions reveals several features like short reaction time compared to the conventional heating, ease of work-up after the reaction, and reduction in usual thermal degradation and better selectivity. Microwave heating has been proved to be beneficial particularly for the reactions under dry media (i.e. in the absence of solvent, on solid support with or without catalysts). More recently Varma *et al.*⁸ have reported the preparation of Mannich reactions using microwave irradiation, which prompted us to present our results on the synthesis of benzofuran Mannich bases under

p-toluene sulfonic acid or phase transfer catalytic conditions in domestic microwave oven.

Experimental Section

The melting points were determined by using polmon melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer and ¹H NMR spectra were recorded on Varian Gemini 200 MHz spectrophotometer, mass spectra was recorded on EIMS 70eV. The purity of compounds was checked by TLC on silica gel G plates using benzene-methanol (2:1), iodine as a visualizing agent. The reactions were carried out in BPL 800-G domestic microwave oven.

General procedure for the preparation of Mannich bases

Conventional method. (i) PTSA method. 1-(2-benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-morpholin-4-yl-propan-1-one **3a**. 2-Aroyle-3-methyl-5-acetyl-6-hydroxy benzofuran⁹ (2.94 g, 0.01 mole), paraformaldehyde (0.3 g, 0.01 mole), morpholine hydrochloride (2.47 g, 0.02 mole), PTSA (0.03 g, 0.0002 mole) and isopropyl alcohol (15 mL) were refluxed for 15 hr and the reaction was monitored by TLC. The solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product, yield 60%.

(ii) PTC method. To a magnetically stirred solution of 2-aroyle-3-methyl-5-acetyl-6-hydroxy benzofuran (2.94 g, 0.01mole), paraformaldehyde (0.3 g, 0.01 mole) in 30 mL benzene, 30 mL water and 100 mg TBAHS were added. To this morpholine hydrochloride (2.47 g, 0.02 mole) dissolved in ethylene dichloride was added dropwise over a period of 30 min. The reaction mixture was refluxed for 24 hr. The organic layer was separated and washed with 5% NaOH solution and then with water. The resulting organic layer was dried over anhydrous sodium sulphate. The excess solvent was removed under reduced pressure to give an oily residue, which was purified by column chromatography (1:9; methanol - ethyl acetate), yield 65%.

Microwave irradiation method. (i) PTSA method. 2-Aroyle-3-methyl-5-acetyl-6-hydroxybenzo-

furan (2.94 g, 0.01 mole), paraformaldehyde (0.3 g, 0.01 mole), morpholine hydrochloride (2.47 g, 0.02 mole) and PTSA (0.03 g, 0.0002 mole) were thoroughly mixed and placed in a conical flask and the mixture was irradiated for 8 min in microwave oven at 450 watts (**Table I**). The reaction was monitored by TLC after every minute of irradiation. The mixture was then cooled to 25-30°C and a gummy material was crystallized from isopropyl alcohol as a hydrochloride salt, yield 72%.

(ii) **PTC method.** 2-Aroyl-3-methyl-5-acetyl-6-hydroxybenzofuran (2.94 g, 0.01 mole), paraformaldehyde (0.3 g, 0.01 mole), morpholine hydrochloride (2.47 g, 0.02 mole) and PTC (TBAF'S, 100 mg) were thoroughly mixed and placed in a conical flask and the mixture was irradiated for 12 min in a microwave oven at 450 watts (**Table I**). The reaction was monitored by TLC after every minute of irradiation. Then the mixture was cooled to 25-30°C and a gummy material was crystallized from isopropyl alcohol as a hydrochloride salt, yield 70%; IR: 1685 (C=O), 1675 (C=O), 3450 (OH), 690 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O

exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 3.6-3.4 (m, 4H, O-CH₂), 2.8-2.3 (m, 6H, N-CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂); MS: m/z 394 (M+1); Anal. Calcd for C₂₃H₂₃NO₅: C, 70.22; H, 5.89; N, 3.56. Found: C, 70.20; H, 5.85; N, 3.60%.

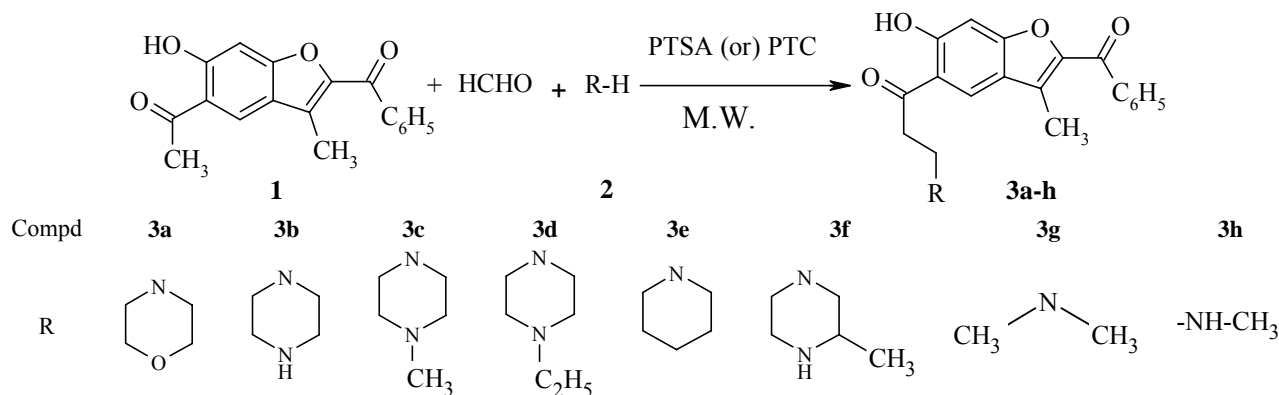
Compounds **3b-h** (**Scheme I**) were prepared similarly.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-(piperazin-4-yl)propan-1-one 3b: IR: 1695 (C=O), 1685 (C=O), 3450 (OH), 699 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 2.6-2.2 (m, 10H, CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂), 1.3 (s, 1H, NH); MS: m/z 393 (M+1); Anal. Calcd for C₂₃H₂₄N₂O₄: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.50; H, 6.10; N, 7.30%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-(4-methyl-piperazin-4-yl)propan-1-one 3c: IR: 1695 (C=O), 1685 (C=O), 3450 (OH), 699 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H),

Table I— Results and conditions of the synthesis of benzo [b]furan Mannich bases **3a-h**

Compd	Conventional method				Microwave irradiation				m.p. °C
	PTSA		PTC		PTSA		PTC		
	Time (hr)	Yield (%)	Time (hr)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	
3a	15	60	24	65	8	72	12	70	275 -80
3b	17	55	28	60	10	71	15	72	300-02
3c	18	58	22	66	12	71	14	82	263-68
3d	18	59	26	68	9	72	18	84	275 -80
3e	15	60	24	62	8	78	12	72	255 -60
3f	16	54	26	60	10	70	14	78	280 -85
3g	16	56	23	63	12	71	10	81	190 -95
3h	17	59	25	60	10	72	12	70	182 -85



Scheme I

7.5-7.29 (m, 5H, Ar-H), 2.6-2.3 (m, 10H, N-CH₂), 2.3 (s, 3H, N-CH₃), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂); MS: m/z 407 (M+1); Anal. Calcd for C₂₄H₂₆N₂O₄: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.00; H, 6.40; N, 6.90%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-(4-ethyl-piperazin-4-yl)propan-1-one 3d: IR: 1695 (C=O), 1685 (C=O), 3450 (OH), 699 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 2.6-2.3 (m, 12H, N-CH₂), 2.8 (s, 3H, -CH₃), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂); MS: m/z 421 (M+1); Anal. Calcd for C₂₅H₂₈N₂O₄: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.5; H, 6.50; N, 6.60%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-(piperidin-4-yl)propan-1-one 3e: IR: 1695 (C=O), 1685 (C=O), 3450 (OH), 699 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 2.9-2.3 (m, 6H, N-CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂), 1.3-1.2 (m, 6H, -CH₂); MS: m/z 392 (M+1); Anal. Calcd for C₂₄H₂₅NO₄: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.00; H, 6.50; N, 6.60%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-(2-methyl-piperazin-4-yl)propan-1-one 3f: IR: 1675 (C=O), 1685 (C=O), 3440 (OH), 690 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 4.5 (m, 1H, -CH) 2.9-2.6 (m, 4H, N-CH₂), 2.4-2.2 (m, 4H, N-CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂), 1.3 (s, 1H, NH), 1.2 (d, J=8Hz, 3H, CH₃); MS: m/z 407 (M+1); Anal. Calcd for C₂₄H₂₆N₂O₄: C, 70.92; H, 6.45; N, 6.89. Found: C, 71; H, 6.7; N, 6.90%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-dimethylaminyl-propan-1-one 3g: IR: 1675 (C=O), 1685 (C=O), 3440 (OH), 690 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 2.6 (s, 6H, N-CH₃), 2.5-2.3 (m, 2H, N-CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H,

CH₂); MS: m/z 352 (M+1); Anal. Calcd for C₂₁H₂₁NO₄: C, 71.78; H, 6.02; N, 3.99. Found: C, 66.00; H, 5.50; N, 3.70%.

1-(2-Benzoyl-6-hydroxy-3-methyl-benzofuran-5-yl)-3-methylaminyl-propan-1-one 3h: IR: 1675 (C=O), 1685 (C=O), 3440 (OH), 690 cm⁻¹ (Ar); ¹H NMR (CDCl₃): δ 11.58 (bs, 1H, C₆-OH, D₂O exchangeable), 7.9 (s, 1H, C₇-H), 7.7 (s, 1H, C₄-H), 7.5-7.29 (m, 5H, Ar-H), 2.8 (s, 3H, N-CH₃), 2.5-2.3 (m, 2H, N-CH₂), 1.8 (s, 3H, C₃-CH₃), 1.4 (t, 2H, CH₂), 1.3 (bs, 1H, NH); MS: m/z 337 (M+); Anal. Calcd for C₂₀H₁₉NO₄: C, 71.20; H, 5.68; N, 4.15. Found: C, 65.50; H, 5.20; N, 3.87%.

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