One-pot synthesis of novel symmetric 1,5-di(benzofuran-2-yl)-3-(4-substituted-aryl)-pentane-1,5-dione derivatives

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Received 7 May 2013; accepted (revised) 17 January 2014

Salicylaldehyde and its substituted derivatives on reaction with bromoacetone under basic condition in ethanol afford corresponding benzofuran derivatives 1a-d. The compounds 1a-d on treatment with different para substituted aromatic aldehydes in presence of base and minimum amount of acetonitrile upon grinding at room temperature gives corresponding α,β-unsaturated carbonyl compounds by crossed aldol condensation, which further undergo Michael addition with 2-acetyl benzofuran to give a new class of symmetric 1,5-di(benzofuran-2-yl)-3-(4-substituted-aryl)-pentane-1,5-dione derivatives 2a-p in one step. The structures of all the newly synthesized compounds have been established by spectral studies.

Keywords: Benzofuran, solvent free condition, crossed aldol condensation, α,β-unsaturated carbonyls, Michael addition, 1,5-dicarbonyl derivatives, one pot synthesis

The benzofuran ring system itself is a common structure element that appears in a large number of medicinally important compounds1. The benzofuran nucleus is widely distributed in natural products particularly among plant kingdom. Benzofuran derivatives are known to possess hypotensive, vasodilating and spasmyloytic activities2. Moreover, some derivatives are used as anti-inflammatory, anlagen3,4 and antihistaminic drugs5-7. In addition some benzofuran derivatives show antibacterial activity as well as antiparasitic properties8,9, anti-HIV activities10, antitubercular activity11, anti diabetic activity12, antidepressant activity13, anti-oxidant activity14, anticonvulsant activity15-18, analgesic activity19, antimicrobial activity20,22, and antitumor23,24. Furthermore, recent studies showed that benzofuran ring system fused with heterocyclic moieties exhibit a wide spectra of pharmacological activities and especially antitumor activity25,26.

In addition, chalcones (α,β-unsaturated carbonyl compounds) are very important compounds as a Michael acceptor in organic syntheses. The Michael addition reaction is one of the most fundamental C-C and C-N bond-forming reactions in the synthesis of 1,5-dicarbonyl compounds. 1,5-diketones are extremely important synthetic intermediates in their own right and are desirable starting materials for generating many heterocyclic27,28 and poly functional compounds29,30. The Michael addition benefits from mild reaction conditions, high functional group tolerance, a large host of polymerizable monomers and functional precursors as well as high conversions and favorable reaction rates31. These features make the Michael addition reaction well suited to numerous emerging technologies including biomedical applications such as gene transfection32, cell scaffolds33 and tissue replacements34.

Results and Discussion

In view of the literature survey of benzofuran as a pharmacological agent and on preparation of 1,5-dicarbonyl derivatives, here in the present work we report on one pot synthesis of novel symmetric 1,5-Di(benzofuran-2-yl)-3-(4-substituted-aryl)-pentane-1,5-dione derivatives under solvent free condition which can be useful starting material for the synthesis of heterocyclic and polyfunctional compounds. The synthesis of key starting materials 2-acetylbenzofuran 1a-d from substituted salicylaldehydes with bromoacetone in presence of KOH in ethanol has been well established35. 1,5-Di(benzofuran-2-yl)-3-(4-chloro-phenyl)-pentane-1,5-dione 2a was prepared by grinding 2-acetylbenzofuran and 4-chlorobenzaldehyde (2:1 ratio) in presence of NaOH and minimum amount of acetonitrile as solvent using a mortar and pestle at room temperature (Scheme I). The IR spectrum of 2a exhibited the absorption bands at 3104 cm⁻¹ (Ar-H str), 2925 cm⁻¹ (-CH str), 1680 cm⁻¹ (>C=O str),
1100 cm⁻¹ (C-O-C), indicating the crossed aldol condensation followed by Michel addition. The formation of the new dicarbonyl was further justified by the ¹H NMR spectrum (DMSO-δ₆) appearance of peaks at δ 7.94 (s, 2H, ArH), 7.82-7.85 (d, 2H, ArH, J = 9Hz), 7.68-7.07 (d, 2H, ArH, J = 6 Hz), 7.54 (t, 2H, ArH), 7.36-7.43 (m, 4H, ArH), 7.28-7.31 (d, 2H, ArH, J = 9 Hz), 3.80-4.09 (m, 1H, -CH), 3.46-3.48 (br-s, 4H, -CH₂) were observed. Finally the structure was further authenticated by the LC-MS which shows the m/z peak at 443.1 (M⁺) of 95% purity. Likewise the compounds 2b-p were synthesized by treating 1a-d with various para-substituted aromatic aldehydes under similar experimental conditions. The IR, ¹H NMR and LC-MS spectra of 2b-p were in agreement with their predicted structures.

Materials and Methods

All melting points were determined with open capillary and are uncorrected. IR spectra were recorded in KBr pellets by using JASCO FTIR-4100 spectrophotometer. ¹H NMR spectra were recorded in CDCl₃ and DMSO on JEOL-400 MHz NMR instrument. Chemical shift are reported in δ units relative to TMS as internal standard. Mass spectral data were obtained on AGILENT LC-MS column c-18 instrument. The progresses of all the reactions were monitored by thin layer chromatography.

Experimental Section

General procedure for synthesis of 1-(benzofuran-2-yl) ethanone, 1a

Salicylaldehyde (10 mL, 0.0012 mmol) was taken in 50 mL of absolute ethanol. To this KOH pellets (5.6 g, 0.0012 mmol) were added and reaction mixture was stirred for 15 min on ice bath giving the salt. To this salt bromoacetone (14.3 mL, 0.0012 mmol) was added drop wise for about 20 min in cold condition. Further whole reaction mixture was stirred for 20 min with catalytic amount of potassium iodide (KI). The completion of reaction was monitored by TLC. After complete reaction, the reaction mixture was poured into crushed ice containing sodium chloride. Separated solid was filtered and dried. The product was recrystallized from petroleum ether to get
yellow crystals. The compounds 1b-d were synthesized under similar reaction conditions.

**General procedure for synthesis of 1,5-di(benzofuran-2-yl)-3-(4-chloro-phenyl)-petane-1,5-dione, 2a**

2-Acetylbenzofuran 1a (0.5 g, 0.0062 mmol), 4-chlorobenzaldehyde (0.33 g, 0.0031 mmol) and NaOH (0.24 g, 0.0062 mmol) were thoroughly mixed and well ground using a mortar and pestle with minimum amount of acetonitrile, a yellow medium was aggregated giving a yellow coloured powder product (about 30 min). The reaction product was poured into ice cold water, yellow coloured solid which separated out was filtered and dried. The crude product was subjected to column chromatography on silica gel (60-120 mesh) using a mixture of pet ether and ethyl acetate (9:1) as an eluent to obtain compound 2a. The compounds 2b-p were synthesized under similar reaction conditions. The characterization data of the synthesized compounds are reported in Table I.

**Spectral Data**

1-(Benzofuran-2-yl)ethanone, 1a. IR (KBr): 3120 (Ar-H str), 2922 (CH str), 1672 >C=O str, 1077-1174 C-O-C; 1H NMR (400 MHz, CDCl3): δ 8.00 (s, 1H, ArH), 7.57 (dd, 1H, ArH, J = 7.60 Hz), 7.48 (t, 2H, ArH, J = 6.85 Hz), 2.61 (s, 3H, -CH3); MS: m/z 224 (M+1), 242 (isotopic peak).

1-(5-Bromo-benzofuran-2-yl)ethanone, 1b. IR (KBr): 3104 (Ar-H str), 2922 (CH str), 1667 >C=O str, 1078-1174 C-O-C; 1H NMR (400 MHz, CDCl3): δ 8.00 (s, 1H, ArH), 7.57 (dd, 1H, ArH, J = 7.60 Hz), 7.48 (t, 2H, ArH, J = 6.85 Hz), 2.61 (s, 3H, -CH3); MS: m/z 240 (M+1), 242 (isotopic peak).

1-(5-Chloro-benzofuran-2-yl)ethanone, 1c. IR (KBr): 3104 (Ar-H str), 2921 (CH str), 1665 >C=O str, 1081-1174 C-O-C; 1H NMR (400 MHz, CDCl3): δ 8.00 (s, 1H, ArH), 7.57 (dd, 1H, ArH, J = 7.60 Hz), 7.48 (t, 2H, ArH, J = 6.85 Hz), 2.61 (s, 3H, -CH3); MS: m/z 195.1 (M+1).

1-(5-Nitro-benzofuran-2-yl)ethanone, 1d. IR (KBr): 3114 (Ar-H str), 2922 (CH str), 1665 >C=O str, 1472, 1320 (Ar-N=O str), 1078-1174 C-O-C; 1H NMR (400 MHz, CDCl3): δ 8.00 (s, 1H, ArH), 7.57 (dd, 1H, ArH, J = 7.60 Hz), 7.48 (t, 2H, ArH, J = 6.85 Hz), 2.61 (s, 3H, -CH3). MS: m/z 206.16 (M+1).

1,5-Di(benzofuran-2-yl)-3-(4-chlorophenyl)pentane-1,5-dione, 2a. IR (KBr): 3104 (Ar-H str), 2925 (>C=O str), 1680 >C=O str), 1100 (C-O-C); 1H NMR (300 MHz, DMSO-d6): δ 7.94 (s, 2H, ArH), 7.82-7.85 (d, 2H, ArH, J = 9 Hz), 7.68-7.07 (d, 2H, ArH, J = 6 Hz), 7.54 (t, 2H, ArH), 7.36-7.43 (m, 4H, ArH), 7.28-7.31 (d, 2H, ArH, J = 9 Hz), 7.53 (t, 2H, ArH, J = 7.05 Hz), 2.61 (s, 3H, -CH3); MS: m/z 443.1 (M+1), 446.1 (isotopic peak).

1,5-Di(benzofuran-2-yl)-3-phenyl-pentane-1,5-dione, 2b. IR (KBr): 3120 (Ar-H str), 2926 (>CH str), 1652 >C=O str), 1080-1095 (C-O-C); 1H NMR (300 MHz, DMSO-d6): δ 7.94 (s, 2H, ArH), 7.83 (d, 2H, ArH, J = 6 Hz), 7.68-7.70 (d, 2H, ArH, J = 6 Hz), 7.55 (t, 2H, ArH), 7.35-7.44 (m, 5H, ArH), 7.30 (d, 2H, ArH, J = 8.50 Hz), 3.80-4.08 (m, 1H, -CH), 3.47 (br-s, 4H, -CH2); MS: m/z 409.4 (M+1).

5-Di(benzofuran-2-yl)-3-(4-methoxyphenyl)pentane-1,5-dione, 2c. IR (KBr): 3113 (Ar-H str), 2922 (>C=O str), 1667 >C=O str), 1070-1095 (C-O-C); 1H NMR (300 MHz, DMSO-d6): δ 7.94 (s, 2H, ArH), 7.84 (d, 2H, ArH, J = 9.10 Hz), 7.79 (d, 2H, ArH, J = 6.2 Hz), 7.54 (t, 2H, ArH), 7.35-7.47 (m, 4H, ArH), 7.29 (d, 2H, ArH, J = 8.54 Hz), 3.9-4.10 (m, 1H, -CH), 3.76 (s, 3H, -OCH3), 3.45 (br-s, 4H, -CH2); MS: m/z 439.4 (M+1).

1,5-Di(benzofuran-2-yl)-3-(4-nitrophenyl)pentane-1,5-dione, 2d. IR (KBr): 3110 (Ar-H str), 2922 (>C=O str), 1666 >C=O str), 1095 (C-O-C); 1H NMR (300 MHz, DMSO-d6): δ 8.00 (s, 2H, ArH), 7.85 (d, 1H, Ar-H, J = 7.56 Hz), 7.45-7.50 (m, 2H, Ar-H), 7.33 (t, 1H, Ar-H, J = 7.07 Hz), 2.61 (s, 3H, -CH3); MS: m/z 161.17 (M+1).

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1,5-Di(5', 5'-bischlorobenzofuran-2-yl)-3-(4-chlorophenyl)pentane-1,5-dione, 2g. IR (KBr): 3104 (Ar-H str), 2927 (-CH str), 1652 (>C=O str), 1080-1098 (C-O-C); \(^1^H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.95 (s, 2H, ArH), 7.81-7.83 (d, 2H, ArH, J = 6 Hz), 7.73 (d, 2H, ArH, J = 8.5 Hz), 7.59 (t, 2H, ArH), 7.34 (d, 2H, ArH, J = 7.65 Hz), 7.29-7.32 (2H, ArH, J = 9 Hz), 3.8-4.08 (m, 1H, -CH), 3.78 (s, 3H, -OCH\(_3\)), 3.48 (br-s, 4H, -CH\(_2\)); MS: \(m/z\) 597.2 (M+1), 599.2 (isotopic peak).

1,5-Di(5', 5'-bischlorobenzofuran-2-yl)-3-(4-methoxyphenyl)pentane-1,5-dione, 2f. IR (KBr): 3104 (Ar-H str), 2927 (-CH str), 1655 (>C=O str), 1080-1098 (C-O-C); \(^1^H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.97 (s, 2H, ArH), 7.81-7.83 (d, 2H, ArH, J = 6 Hz), 7.72 (d, 2H, ArH, J = 8.5 Hz), 7.59 (t, 2H, ArH), 7.34 (d, 2H, ArH, J = 7.65 Hz), 7.29-7.32 (2H, ArH, J = 9 Hz), 3.8-4.08 (m, 1H, -CH), 3.78 (s, 3H, -OCH\(_3\)), 3.48 (br-s, 4H, -CH\(_2\)); MS: \(m/z\) 601.6 (M+1), 603.6 (isotopic peak).

1,5-Di(5', 5'-bischlorobenzofuran-2-yl)-3-(4-nitropheny)pentane-1,5-dione, 2g. IR (KBr): 3104 (Ar-H str), 2927 (-CH str), 1655 (>C=O str), 1080-1098 (C-O-C); \(^1^H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.10 (s, 2H, ArH), 7.90-7.94 (d, 2H, ArH, J = 12 Hz), 7.79-7.82 (d, 2H, ArH, J = 9 Hz), 7.62 (t, 2H, ArH), 7.42 (d, 2H, ArH, J = 7.07 Hz), 7.32-7.35 (d, 2H, ArH, J = 9 Hz), 4.08 (m, 1H, -CH), 3.46-3.48 (br-s, 4H, -CH\(_2\)); MS: \(m/z\) 523.3 (M+1), 525.3 (isotopic peak).

1,5-Di(5', 5'-bischlorobenzofuran-2-yl)-3-(4-nitropheny)pentane-1,5-dione, 2m. IR (KBr): 3115 (Ar-H str), 2926 (-CH str), 1659 (>C=O str), 1085-1095 (C-O-C); \(^1^H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.45 (s, 2H, ArH), 7.94-7.98 (d, 2H, ArH, J = 12 Hz), 7.80-7.83 (d, 2H, ArH, J = 9 Hz), 7.68 (t, 2H, ArH), 7.50 (m, 3H, ArH, J = 6.5 Hz), 7.40-7.42 (d, 2H, ArH, J = 8.5 Hz), 3.80-4.08 (m, 1H, -CH), 3.45-3.47 (br-s, 4H, -CH\(_2\)); MS: \(m/z\) 499.4 (M+1).
δ 8.46 (s, 2H, ArH), 7.95-7.99 (d, 2H, ArH, J = 12 Hz), 7.86-7.89 (d, 2H, ArH, J = 9 Hz), 7.70 (t, 2H, ArH), 7.42 (d, 2H, ArH, J = 6.5 Hz), 7.40-7.43 (d, 2H, ArH, J = 8.5 Hz), 3.83-4.10 (m, 1H, -CH), 3.78 (s, 3H, -OCH3), 3.46-3.48 (br-s, 4H, -CH2); MS: m/z 529.4 (M+1),

1,5-Dithio(-bisnitrobenzofuran-2-yl)-3-(4-nitro-phenyl)-pentane-1,5-dione, 2p (C-O-C); thiopyryliums. The procedure that allows the one-pot preparation 1,5-dione derivatives of benzofuran from 2-acetyl benzofuran by aldol condensation followed by Michael addition has been demonstrated. The developed methodology is simple, non-hazardous and economic too. The research could be extended for the synthesis of new benzofuran derivatives, fused with other heterocycles such as pyridines, pyrylium and thiopyryliums.

Conclusion

The authors are thankful to University College of Science and Tumkur University for providing the laboratory facilities. Authors are also thankful to the Department of Science and Technology, New Delhi, Government of India for providing financial assistance to carry out the project.

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References