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SYNTHESIS OF 2-AROYLBENZOFURAN-3-OLS BY DIECKMANN REACTION CONDITIONS AND ITS ANTIBACTERIAL ACTIVITIES. `

Sangram Patil *, Pushpendra Tiwari

Department of Chemistry, Mansarovar Global University , Sehore ,466111.

Abstract: Several 2-aroylbenzofuran-3-ols were synthesized by applying Dieckmann reaction conditions on substituted methylsalicylates with 2-bromo-1-aroylethanones and base in ultrasonic wave conditions. Comparison study of ultrasonic conditions and normal Dickman reaction condition studied. Synthesized compounds were tested for their antibacterial activity.

Index Terms - 2-**aroylbenzofuran-3-ols; cyclization; Dieckmann reaction, ultrasonic waves, antibacterial activity.**

I. INTRODUCTION

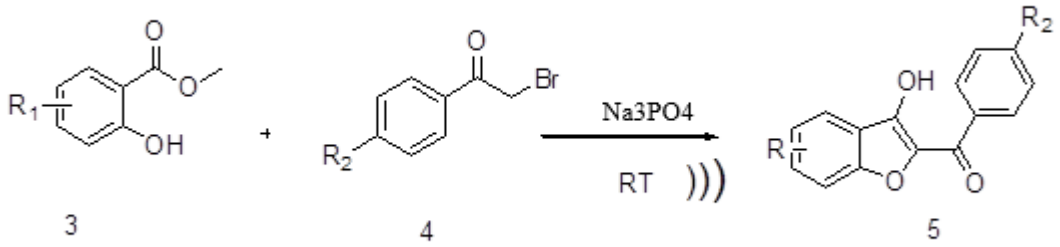
Benzofuran derivatives are a basic structural component in a diversity of biologically active natural products as well as synthetic materials.[1] Benzofuran derivatives possess several biological properties such as anti-inflammatory, antimicrobial, antifungal, antihyperglycemic, analgesic, antiparasitic, and antitumor activities. [2-7-]. Several benzofuran derivatives have been prepared and introduced as antibacterial agents. [8-15] owing to the prodigious biological position of this scaffold, examination of various approaches for synthesis and structural alteration of benzofuran derivatives have nowadays become a significant area of research. Aroylbenzofuran-3-ol are useful synthetic intermediates for many drugs [16]. Tautomer's of bezofuran-3-ols can be prepared by several methods including the classic Dieckmann condensation of methyl 2-(2-oxo-2-aroyl-benzoates, [17] cyclocondensation of 2-aroylacetylphenol by bromination and rearrangement of 3-haloflavones, [18] oxidative cyclization of 2-aroylacetylphenol, [19] as well as biotransformation of 2-hydroxychalcones in cell suspension cultures [20]. Patil et.al synthesized benzofuran derivatives using basic ionic liquid [21]. However, most of these methods have limited application because of the poor availability of starting material and low yields. Ultrasound-assisted organic synthesis is an advantageous "green" methodology, which is very useful in practical organic synthesis [22]. conventional energy sources like light, heat, pressure, and energy per molecule. are used as regular sources for organic reactions but Ultrasound irradiation is a different type of energy source than available sources. The practice of ultrasound waves in synthetic organic chemistry has been a subject of interest and increased the attention of researchers during the last decades. Ultrasound waves have been used to carry out different types of chemical reactions in chemistry, heterocyclic chemistry and medicinal chemistry like condensation reactions, substitution reactions, oxidation, reduction, addition reactions, photochemical reactions, protection and deprotection reactions, coupling reactions, polymerization reactions etc. [23]. Due to using of ultrasonic conditions for organic reactions, we get high efficiency, low waste in reaction and require low energy. Sonochemistry uses energy in the region of 20 kHz to 1 MHz and has been successfully used in reactions due to its high energy and the skill to diffuse reagents in small particles and quicken the rate of reaction.

Synthesis of benzofuran derivatives require extended reaction time and toxic reagents that are not commercially available. Therefore, we decided to use ultrasonic conditions to synthesize the compounds. Looking at the broad spectrum of activities to these compounds we decided to evaluate the antibacterial and antifungal activities of these compounds.

II. RESULTS AND DISCUSSION

Chemistry:

We studied the representative reaction for preparation of 5a from methylsalycylate (**3**) and phenacyl bromide (**4**) using Dickman condition and ultrasonic wave condition in acetone. (**Scheme1**)



Scheme-2 Synthesis of 2- aroylbenzofuran-3ols

We studied the representative reaction for preparation of 5a from methylsalycylate (3) and phenacyl bromide (4) in acetone using Na3PO4 at 60 deg and under ultrasonic conditions at room temperature. The optimal reaction conditions were developed using the different combination of solvent. By using acetone as solvent at room temperature for 20 minutes using ultrasonic conditions. 2-Benzoylbenzofuran-3-ol 5a was obtained in 32 % yield. Desired structure was determined by NMR and Mass spectra. By using the traditional Dickman reaction conditions yield is 82%. Effect of solvent and irradiation time checked using solvents like tetrahydrofuran, acetonitrile, Acetone, the desired product 5a was obtained in 52%, 51%, 32%, respectively. Same reactions were carried out by using normal Dickman conditions required 4-8 hrs for completion of reaction.

When we irradiated same reaction mixture in absence of solvent sonicated at 250C, yield of the product was enhanced melodramatically to 90%. This clearly indicating that ultrasonic waves conditions are useful and save the solvent and reaction time. The condensation product isolated by simply pouring reaction mixture in water in good yields the results were shown in Table 1.

Table 1 Optimization of reaction condition

Solvent	Reaction time	% yield
THF	20 min	52
ACN	20 min	51
Acetone	20 min	32
As such	20 min	92

Under these optimized conditions we used same reaction conditions for synthesis of various 2-Aroylbenzofuran-3-ols (5) as shown in Table 3 various substituted Phenacyl bromide and methyl salicylate were used as reaction substrates and sodium phosphate under ultrasonic waves afforded the corresponding aroylbenzofuran-3-ols (5) derivatives in excellent yields regardless of the different substitution on the aromatic ring of the substrates.

Substrates possessing electron-donating group on the aromatic ring of the methylsalycylate (3), exhibited better yields than electron-withdrawing group,

Table 2. Comparative yields of Aroylbenzofuran-3-ols, & Dickman reaction

Comp.no.	R1	R2	%yield Ultrasonic conditions	%yield Dickman reaction
5a	H	H	94	40
5b	H	CH3	90	32
5c	H	Cl	87	25
5d	H	OMe	90	22
5e	5-OMe	OMe	91	22
5f	5-OMe	CH3	83	21
5g	5-OMe	H	92	30
5h	5-OMe	Cl	90	34
5i	3-Nitro	OMe	73	14
5j	3-Nitro	CH3	71	11
5k	3-Nitro	H	69	10
5l	3-Nitro	CH3	74	11

The synthesized compounds were evaluated for their in vitro antimicrobial activity against Gram-positive bacteria: Staphylococous aureus (NCLM- 2602), Bacillus subtillis (NCLM- 2458), Gram negative Escherichiacoli (NCLM- 2809) and fungal strain Aspergillus niger (NCLM- 617), Rhizopus otyzae (NCLM- 1299).
The antimicrobial activity of the compuond was assessed by antimicrobial susceptibilty test [24]. 100 µl of 24h growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for Escherichia coli) and potato dextrose agar for fungi, in Petri plates. 50 µl compound at the concentration of 100 µg/ml in DMSO saturated on discs of 6mm diameter were kept on agar surface. The plates refrigerated for two hours to allow prediffusion of the compound from the discs in to the seeded agar layer and then incubated at 37 0C for 24h for bacteria and 28 0C for 48h for fungi. Zones of inhibition were measured in mm and size of the disc was subtracted from the zone size to measured final activity. DMSO saturated discs served as solvent control or negative control and Streptomycin saturated discs (30 µg) for bacteria and Nystatin (30 µg) for fungi as a reference or positive control. The MIC for the synthesized compound was given in table 2

Comp. No.	Zone of Inhibition (mm)				
	Bacteria			Fungi	
	S. A. NCLM No.2602	B. S. NCLM No.2458	E. C. NCLM No.2809	A. N. NCLM No.617	R.O. NCLM No.1299
5a	2.7	3.4	3.6	3.1	5.2
5b	4.3	2.9	3.1	2.0	1.9
5c	5.0	5.5	5.8	6.6	4.91
5d	7.2	7.7	6.61	5.9	4.7
5e	11.1	10.9	9.1	8.5	6.91
5f	7.4	7.8	6.4	5.9	5.15
5g	8.19	8.0	7.4	6.5	5.6
5h	7.2	7.2	8.9	7.7	4.3
5i	11.8	11.2	9.1	8.5	6.91
5j	5.9	6.0	6.7	7.1	5.81
5k	10.1	8.7	8.18	7.9	5.7
5l	7.7	6.4	7.0	5.0	6.0
Standard	12	10	11	10	9

- *S.A.- Staphylococcus aureus, B.S.- Bacillus subtilis, E.C.- Escherichia coli, A.N. Aspergillius Niger, R. O.- Rhizopus Ostoyae.*
- These results are average results of four experiments.
- These compounds were used at concentration of 100 µg/mL.
- Streptomycin for bacteria and Nystain for fungi were used as standard at concentration of 30 µg.

All the Aroylbenzofuran-3-ols (5-a-j) were evaluated for antibacterial and antifungal activity. All these compounds were found to exhibit moderate to good antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (Table 2) it was observed that among all the compounds tested, compounds 5(a-j) shows moderate activity against all the tested bacteria and fungi. Compound 5e,5j showed moderate activity against all bacteria. Compound 5e and 5j also showed moderate activity against fungi. Among all tested bacteria and fungi, compounds 5e and 5j showed good activity against staphylococcus aureus, Bacillus subtillis and Escherichia coli. Among the other compounds 5i, 5k and 5e shown good activity against all the bacteria. and good activity against Aspergillus Niger and Rhizopus Ostoyae fungi. Among all the compounds 5j and 5k was found to be most active compound.

III.CONCLUSION

In conclusion, We have developed environmental friendly new single step method for the synthesis of aroylbenzofuran-3-ols using ultrasonic wave conditions without solvent medium as well. Present methodology offers benefits such as easily available material and less reaction time and saving of solvent cost for the reaction. We also evaluated the antibacterial and antibacterial potential of the b Aroylbenzofuran-3-ols (5-a-j) and found to be active against the tested bacteria.and fungi .

IV.EXPERIMENTAL

Methods

General Procedure for preparation of 2-Aroylbenzofuran-3-ols

To a solution of Phenacyl bromide (1.09 g, 5.5 mmol) and methyl salicylate (0.76 g, 5.0 mmol), sodium phosphate(0.1mole%) in a test tube, and the resulting reaction mixture was kept in ultrasonic wave conditions for 20 min. After completion of the reaction (by confirming using TLC), cold water was added to reaction mixture and stirred for 10 min to get solid compound which was filtered and filtrate was removed, obtained solid was washed with 1N HCl and dried under vacuum to get pure product.

Analytical data of selected compounds.

2-Benzoylbenzofuran-3-ol (5a):

1H NMR (400 MHz, CDCl3): δ: - 7.30 (t, J = 7.2 Hz, 1H,), 7.46 (d, J =8.8 Hz, 1H), 7.53-7.57 (m, 3H), 7.61 (t, J = 6.6Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 8.0 Hz, 2H), 11.04 (s, 1H, OH).

2-(4-Methylbenzoyl) benzofuran-3-ol (5b):
1H NMR (400 MHz, d6-DMSO): δ:- 2.33 (s, 3H), 6.97 (t, J =7.2 Hz), 7.11 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.30(t, J = 7.2 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H).
2-(4-Chlorobenzoyl) benzofuran-3-ol (5c):
1H NMR (400 MHz, d6-DMSO): δ: - 7.13-7.19 (m, 1H), 7.47-7.51 (m, 2H), 7.52 (d, J = 8.4 Hz), 7.79 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 8.4 Hz).
2-(4-Methoxybenzoyl)benzofuran-3-ol (5d) 1H NMR (300 MHz, CDCl3): δ:- 3.90 (s, 3H), 7.01 (d, J =9.0 Hz, 2H), 7.26~7.32 (m, 1H), 7.45 (d, J = 7.5Hz, 1H), 7.50-7.56(m, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 9.0 Hz, 2H).
2-(4-Methoxybenzoyl)-5-methoxybenzofuran-3-ol (5e): 1H NMR (400 MHz, CDCl3): δ: - 3.89 (s, 3H), 3.90 (s, 3H), 6.90 (m, 2H), 7.04 (m, 2H), 7.65 (d, J = 8.7 Hz, 1H), 8.32 (m, 2H).
2-(4-Methylbenzoyl)-5-methoxybenzofuran-3-ol (5f): 1H NMR (400 MHz, CDCl3): δ: -2.45 (s, 3H), 3.99 (s, 3H), 6.90 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.66 (m, 1H,), 8.19 (d, J = 8.1 Hz, 2H).
2-Benzoyl-5-methoxybenzofuran-3-ol (5h)
1H NMR (400 MHz, CDCl3): δ: - 3.87 (s, 3H), 6.89 (m, 2H), 7.55 (m, 3H), 7.68 (m, 1H, H-1), 8.29 (d, J =7.6 Hz, 2H), 11.36 (s, 1H, OH).

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IV. CONFLICT OF INTEREST

Authors declared that they have no conflict of interest

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