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Research Article

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Synthesis of 2-Aroylbenzofuran-3-ols using basic ionic liquid [bmIm]OH

S. G. Patil*, V.V. Bhadke, R. R.Bagul.

Organic Chemistry Research Laboratory, Maharashtra Udaygiri Mahavidyalay, Udgir-413517, Maharashtra, India

ABSTRACT

Basic ionic liquid catalyzed syntheses of various 2-aroylbenzofuran-3-ols were synthesized by Dieckmann reaction of substituted methylsalicylates with 2-bromo-1-aroylethanones in basic ionic liquid, [bmIm]OH. It acts as a base catalyst.Reusability of catalyst with good yields under green reaction conditions is the salient feature of this synthetic method.

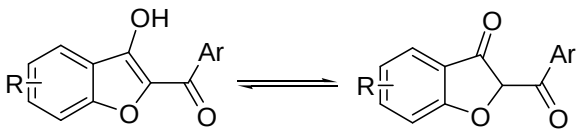
Keywords: 2-aroylbenzofuran-3-ols; cyclization; Dieckmann reaction; [bmIm]OH, base catalyst.

INTRODUCTION

Benzofuran derivatives showed biological activities [1-5-]. Recently 2-aroylbenzofuran-3-ols are reported having excellent anti-inflammatory and antitumor activity activities [6-8]. Aroylbenzofuran-3-ol are useful synthetic intermediates for many drugs [9]. 2-Aroylbenzofuran-3-ols are known to be tautomers of 2-aroylbenzofuran-3-ones (**Scheme I**).

These tautomers can be prepared by several methods including the classic Dieckmann condensation of methyl 2-(2-oxo-2-aroyl-benzoates, [10] cyclocondensation of 2-aroylacetylphenol by bromination and rearrangement of 3-haloflavones, [11] oxidative cyclization of 2-aroylacetylphenol, [12] as well as biotransformation of 2-hydroxychalcones in cell suspension cultures [13] . However, most of these methods have limited application because of the poor availability of starting material and low yields.

In addition, they generally require prolonged reaction time and toxic reagents that are not commercially available. Therefore, during the last few decades, major efforts have been made to develop a straightforward approach for the synthesis of 2-aroylbenzofuran-3-ols from readily available starting materials.



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Scheme-I Tautomers of 2- aroylbenzofuran-3ols

Recently, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media due to its unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapour pressure and ease of recyclability [14-15]. Basic ionic liquids are getting more interest because they showed more advantages such as catalytic efficiency and recyclising of the ionic liquid than the combination of inorganic base and ionic liquid for some base catalyzed processes [16]. A basic ionic liquid [bmIm]OH has been successfully applied to catalyze the Michael addition of active methylene compounds to α, β-unsaturated ketones, esters and nitriles[17] . [bmIm]OH has been extensively applied in different organic reactions such as Heck reaction, Henry reaction, Aldol condensation [18-19], Diels-Alder reaction [20] and heterocyclic synthesis [21].

Knowing all these aspects we have decided to investigate the possibility of formation of 2-Aroylbenzofuran-3-ols using [bmIm]OH as a catalyst.

EXPERIMENTAL SECTION

2.1 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, 5.0mmol) in [bmIm]OH (30 mol %), and the resulting reaction mixture was stirred at50^{0}C till completion of reaction (3-4h). After completion of the reaction (confirm by TLC), cold water added to reaction mixture and stirred for 30 min to get solid compound which was filtered and filterate was removed, obtained solid was washed with 1N HCl dried under vaccume to get pure product. Aqueous layer was evaporated under reduced pressure at 90 ^{o}C to obtain pure ionic liquid.

2.1.1 Analytical data of selected compounds.

2.1.1.1 2-Benzoylbenzofuran-3-ol (5a):

^{1}H 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).

2.1.1.2 2-(4-Methylbenzoyl) benzofuran-3-ol (5b):

^{1}H NMR (400 MHz, *d*6-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).

2.1.1.3 2-(4-Chlorobenzoyl) benzofuran-3-ol (5c):

^{1}H NMR (400 MHz, *d*6-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).

2.1.1.4 2-(4-Methoxybenzoyl)benzofuran-3-ol (5d) ^{1}H 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).

2.1.1.5 2-(4-Methoxybenzoyl)-5-methoxybenzofuran-3-ol (5e): ^{1}H 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).

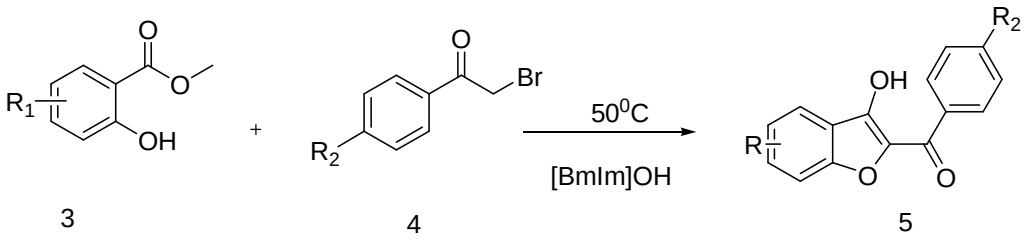
2.1.1.6 2-(4-Methylbenzoyl)-5-methoxybenzofuran-3-ol (5f): ^{1}H NMR (400 MHz, CDCl3): δ: -2.45 (s, 3H), 3.99 (s, 3H), 6.90 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.66 (m, 1H,), 8.19 (d, *J* = 8.1 Hz, 2H).

2.1.1.7 2-Benzoyl-5-methoxybenzofuran-3-ol (5h)

^{1}H 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).

RESULTS AND DISCUSSION

We studied the representative reaction for preparation of 5a from methylsalicylate (3) and phenacyl bromide (4) in Basic ionic liquid [bmIm] OH. (**Scheme2**)



Scheme-2 Synthesis of 2- aroylbenzofuran-3ols

The optimal reaction conditions was developed using the different combination of solvent and mole % [bmIm]OH at room temperature for 4 hour under various conditions. 2-Benzoylbenzofuran-3-ol **5a** was obtained in 27% yield when reaction was carried out using 10mole % [bmIm]OH in DMF at room temperature for 4 hour its structure was determined by NMR and Mass spectra. By using the traditional bases such as, sodium methoxide, KOH forms the desired product in 21 and 32% respectively (table2). When solvents tetrahydrofuran , acetonitrile, acetone, in presence of 10 mole% catalyst, the desired product **5a** was afforded in 52%, 51%, 64%, respectively, Surprisingly with DMF, as solvent the relative yield of the reaction was produced in 27% yield

When we used 30 mole % [bmIm] OH in absence of solvent at 50^0C, yield of the product was improved dramatically to 94%. This clearly indicating that [bmIm]OH served as base in this condensation reaction. The condensation product obtained by simple water work up in good yields the results were shown in **Table 1.**

Table 1 Optimization of reaction condition

Solvent	mole%[bmIm]OH	Reaction time	% yield
DMF	10mole %	3h	27
THF	10mole %	3h	52
ACN	10mole %	3h	51
Acetone	10mole %	3h	64
[bmIm]OH	30mole %	3h	94

Under these optimized conditions we next explored the scope of one pot synthesis of 2-Aroylbenzofuran-3-ols (**5**) as shown in Table 3 various substituted Phenacyl bromide and methyl salicylate were employed as reaction substrates and the reaction can afford the corresponding aroylbenzofuran-3-ols (**5**) derivatives in good yields regardless of the different substitution on the aromatic ring of the substrates..

Table 2. Comparative yields of Aroylbenzofuran-3-ols [bmIm]OH, KOH/Ethanol

	R^1	R^2	%yield [bmIm]OH	%yield Conventional USING KOH\Ethanol
5a	H	H	94	40
5b	H	CH_3	90	32
5c	H	Cl	87	25
5d	H	OMe	90	22
5e	5-OMe	OMe	91	22
5f	5-OMe	CH_3	83	21
5g	5-OMe	H	92	30
5h	5-OMe	Cl	90	34
5i	3-Nitro	OMe	73	14
5j	3-Nitro	CH_3	71	11
5k	3-Nitro	H	69	10
5l	3-Nitro	CH_3	74	11

Substrates with an electron-donating group on the aromatic ring of the methylsalicylate (**3**), for example substrates with methoxy, groups gave good yields than electron-withdrawing group such as, Nitro, simple unsbstituted phenacyl bromide (**4**) and methylsalicylate gave good yields than substituted starting material.

The reusability of ionic liquid was the more advantageous aspect, the ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and reused for the above reactions. We have tested reusability of ionic liquid for compound **5a,** upon use of five times, showed no loss of its activity and does not vary yield notably of final product.

CONCLUSION

We have developed environmental friendly new single step method for the synthesis of aroylbenzofuran-3-ols using reusable basic ionic liquid [bmIm]OH as a catalyst and itself reaction medium as well. Present methodology offer benefits such as easily available catalyst, simple reaction protocol, better yield and reusability of catalyst. This method gives better yield than triethylamine and ammonium acetate method.

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