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N,*N*-Dimethylamino-Functionalized Basic Ionic Liquid Catalyzed One-Pot Multicomponent Reaction for the Synthesis of 4*H*-Benzo[*b*]pyran Derivatives under Solvent-Free Condition

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ABSTRACT: *A simple, clean, and environmentally benign three-component process for the synthesis of 4H-benzo[b]pyran derivatives using basic ionic liquid N,N-dimethylaminoethylbenzyldimethylammonium chloride ($[PhCH_2Me_2N^+CH_2CH_2NMe_2]Cl^-$) as an efficient catalyst under solvent-free condition is described. A wide range of aromatic aldehydes easily undergoes condensation with malononitrile and 5,5-dimethylcyclohexane-1,3-dione (dimedone) under solvent-free condition to afford the desired products of good purity in excellent yields. Taking into account environmental and economical considerations, the protocol presented here has the merits of environmentally benign, simple operation, convenient workup, and good yields.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:91–94, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20516

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INTRODUCTION

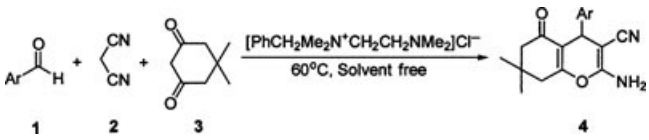
In recent years, 4*H*-benzo[*b*]pyran compounds have attracted much attention due to their wide range of biological and pharmacological activities [1]. It has been reported that benzo[*b*]pyran derivatives have diverse pharmacological activities such as anticoagulant, anticancer, spasmolytic, antiancaphylactia, etc. [2]. In addition, 4*H*-benzo[*b*]pyrans also constitute the structural unit of a series of natural products [3].

Considering the importance of these compounds, many methods for the synthesis of 4*H*-benzo[*b*]pyran derivatives have been reported successively. The conventional synthesis involves the condensation of 5,5-dimethylcyclohexane-1,3-dione (dimedone) with aromatic aldehyde and malononitrile under refluxing DMF [4] or acetic acid [5]. However, these solvents make the workup procedure complicated, lead to poor yields of products, and pollute the environment. The use of microwave [6] and ultrasound irradiations [7] is also reported for the synthesis of pyrans. Recently, many methods have been reported for the preparation of 4*H*-benzo-[*b*]pyrans through two-component [8] or three-component condensation including the use of 4-dodecylbenzenesulfonic acid [9], rare earth perfluorooctanoate ($RE(PFO)_3$) [10], $(NH_4)_2HPO_4$ [11], NaBr [12], tetramethyl ammonium hydroxide [13], basic ionic liquid ($[b\text{mim}]^+OH^-$) [14],

N-methylimidazole [15], (*S*)-proline [16], etc., as catalysts have been introduced for the synthesis of 4*H*-benzo[*b*]pyrans. In spite of the merits of these procedures, each of them suffers at least from one of the following limitations: low yields, unavailability of the reagents, long reaction times, effluent pollution, harsh reaction conditions, and tedious workup procedures. As part of our program aimed at developing new, synthetic, and useful methodologies based on the use of functionalized ionic liquid as catalyst for the preparation of various biologically active heterocyclic compounds, we now report a highly efficient procedure for the preparation of 4*H*-benzo[*b*]pyrans via a one-pot, three-component tandem Knoevenagel cyclocondensation reaction using basic ionic liquid catalyst, *N*,*N*-dimethylaminoethylbenzyldimethylammonium chloride as catalyst under solvent-free conditions.

RESULTS AND DISCUSSION

Initially, we investigated the condensation reaction of 4-nitrobenzaldehyde (**1a**), malononitrile (**2**), and 5,5-dimethylcyclohexane-1,3-dione (**3**) in the presence of 5 mol% of *N*,*N*-dimethylaminoethylbenzyldimethylammonium chloride under solvent-free condition at 60°C for 30 min. It was found that *N*,*N*-dimethylaminoethylbenzyldimethylammonium chloride showed excellent catalytic activity; the reaction proceeded very smoothly and gave the product **4a** in 94% yield (Table 1, entry 1). No product was detected in the absence of the catalyst, and it showed that the catalyst was essential in the reaction. Encouraged by this result, we further demonstrated the scope and generality of the present method by the reaction of various aldehydes (**1**) with malononitrile (**2**) and dimedone (**3**) under the above-mentioned unoptimum conditions (Scheme 1). In all cases, good yields with good selectivity were obtained. All of the results are shown in Table 1.



SCHEME 1

As can be seen from Table 1, in all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. The aromatic aldehydes bearing electron-donating groups (such as *N*,*N*-dimethylamino group, hydroxyl group, methoxyl group, and methyl group) required a longer reaction time and gave lower yields than those bearing electron-withdrawing groups (such as the nitro group, halide; Table 1, entries 7–10). It is worthy of note that the reaction proceeded without the protection of acidic hydroxyl substituents (Table 1, entry 9).

One of the main aims of our study was to investigate the reuse and recycling of the ionic liquid catalyst. The catalyst was easily recovered by the removal of the methanol filtrate after filtering off the products. Reusabilities of the catalyst were examined with the reaction of 4-nitrobenzaldehyde (**1a**), malononitrile (**2**), and dimedone (**3**) for the model reaction. It can be seen from Fig. 1 that the catalyst could be run for five times without the loss of the activities.

CONCLUSION

In conclusion, we have described a practical and efficient procedure for the preparation of 4*H*-benzo[*b*]pyrans through the three-component

TABLE 1 Synthesis of 4*H*-Benzo[*b*]pyrans Catalyzed by *N*,*N*-dimethylaminoethylbenzyldimethylammonium Chloride under Solvent-Free Condition[a]

Entry	*Ar*	*Time (min)*	*Product*	*Yield (%)*[b]
1	4-NO_2-C_6H_4	30	**4a**	94
2	3-NO_2-C_6H_4	30	**4b**	92
3	2,4-2Cl-C_6H_3	30	**4c**	89
4	4-Cl-C_6H_4	30	**4d**	91
5	4-Br-C_6H_4	50	**4e**	83
6	C_6H_5	30	**4f**	76
7	4-Me_2N-C_6H_4	80	**4g**	73
8	4-MeO-C_6H_4	50	**4h**	85
9	4-HO-C_6H_4	35	**4i**	86
10	4-Me-C_6H_4	30	**4j**	75

[a]Reaction conditions: aromatic aldehyde (1 equiv.), malononitrile (1 equiv.), dimedone (1 equiv.), catalyst (5 mol%), solvent free, 60°C.
[b]Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data.

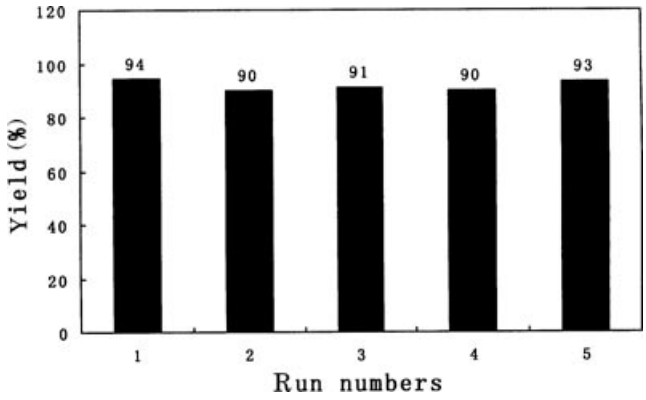


FIGURE 1 Recycling of ionic liquid catalyst.

reaction of aromatic aldehydes, malononitrile, and dimedone by using a catalytic amount of *N,N*-dimethylaminoethylbenzyldimethylammonium chloride as catalyst under solvent-free condition. This procedure offers several advantages including mild reaction conditions, cleaner reaction, satisfactory yields of products, as well as a simple experimental and isolated procedure that makes it a useful and attractive protocol for the synthesis of these compounds.

EXPERIMENTAL

Melting points were measured on an Electrothermal X6 microscopy digital melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Equinox 55 spectrometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in d_6-DMSO on a Bruker AVANCE 300 (300 MHz) instrument with the TMS at δ 0.00 ppm as an internal standard.

Chemicals used were of commercial grade, and they were used without further purification. The ionic liquid *N,N*-dimethylaminoethylbenzyldimethylammonium chloride was prepared according to the method reported in the literature [17].

General Procedure for the Synthesis of 4H-Benzo[b]pyran

An equimolar (3 mmol) mixture of an aromatic aldehyde **1**, malononitrile **2**, dimedone **3** and *N,N*-dimethylaminoethylbenzyldimethylammonium chloride (5 mol%) was vigorously stirred at 60°C for the specific time indicated in Table 1. The end of the reaction was monitored by TLC. Then, the crude product obtained was washed with cold methanol. The resulting solid was purified by recrystallization from hot methanol to afford the pure products **4**.

All of the products are known, and the data are found to be identical with those that are reported in the literature elsewhere. The spectral data of selected products are given below.

2-Amino-3-cyano-4-(4′-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4a**): mp 176–177°C (lit. [12] 177–178°C); FT-IR (KBr): ν: 3408, 3321, 3181, 2187, 1673, 1632, 1597, 1520, 1351, 1216 cm^{-1}; ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.07 (d, $J = 16.1$ Hz, 1H, H-6), 2.23 (d, $J = 16.1$ Hz, 1H, H′-6), 3.58 (s, 2H, CH_2), 4.32 (s, H, CH), 7.41 (d, $J =$ 8.6 Hz, 2H, ArH), 8.14 (d, $J = 8.6$ Hz, 2H, ArH) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz), δ: 27.83 (CH_3), 29.18 (CH_3), 32.74 (C-7), 36.56 (C-4), 40.38 (C-8), 50.75 (C-6), 57.85 (C-3), 112.62 (C-4a), 120.28 (CN), 124.60 (2C=), 129.54 (2C=), 147.15 (C=), 153.22 (C=), 159.49 (C-2), 164.03 (C-8a), 196.63 (C=O) ppm.

2-Amino-3-cyano-4-(4′-chlorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4d**): mp 212–214°C (lit. [12] 215–217°C); FT-IR (KBr) ν: 3382, 3185, 2190, 1676, 1637, 1606, 1366, 1216 cm^{-1}; ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 0.90 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.06 (d, $J = 16.1$ Hz, 1H, H-6), 2.21 (d, $J = 16.1$ Hz, 1H, H′-6), 3.58 (s, 2H, CH_2), 4.15 (s, 1H, CH), 7.13 (d, $J =$ 8.4 Hz, 2H, ArH), 7.31 (d, $J = 8.4$ Hz, 2H, ArH) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz), δ: 27.76 (CH_3), 29.24 (CH_3), 32.72 (C-7), 36.02 (C-4), 40.11 (C-8), 50.83 (C-6), 58.63 (C-3), 113.22 (C-4a), 120.52 (CN), 129.22 (2C=), 130.04 (2C=), 132.03 (C=), 144.68 (C=), 159.40 (C-2), 163.54 (C-8a), 196.61 (C=O) ppm.

2-Amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4f**): mp 222–223°C (lit. [15] 224–225°C); FT-IR (KBr) ν: 3396, 3325, 3211, 2963, 2199, 1664, 1602, 1371, 1214, 1036 cm^{-1}; ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.06 (d, $J = 16.1$ Hz, 1H, H-6), 2.22 (d, $J = 16.1$ Hz, 1H, H′-6), 3.58 (s, 2H, CH_2), 4.13 (s, 1H, CH), 7.09–7.18 (m, 3H, Ar), 7.23–7.28 (m, 2H, ArH) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz), δ: 27.70 (CH_3), 29.34 (CH_3), 32.73 (C-7), 36.5 (C-4), 40.11 (C-8), 50.88 (C-6), 59.18 (C-3), 113.64 (C-4a), 120.69 (CN), 127.50 (C=), 128.08 (2C=), 129.26 (2C=), 145.68 (C=), 159.40 (C-2), 163.42 (C-8a), 196.59 (C=O) ppm.

2-Amino-3-cyano-4-(4′-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4h**): mp 195–196°C (lit. [14] 195–197°C); FT-IR (KBr) ν: 3376, 3327, 3188, 2920, 2194, 1681, 1657, 1607, 1510, 1370, 1254 cm^{-1}. ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 0.90 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.05 (d, $J = 16.1$ Hz, 1H, H-6), 2.21 (d, $J = 16.1$ Hz, 1H, H′-6), 3.58 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.08 (s, 1H, CH), 6.81 (d, $J =$ 8.6 Hz, 2H, ArH), 7.01 (d,

$J =$ 8.6 Hz, 2H, ArH) ppm. ^{13}C NMR (d_6-DMSO, 75 MHz), δ: 27.70 (CH_3), 29.34 (CH_3), 32.73 (C-7), 36.50 (C-4), 40.11 (C-8), 51.07 (C-6), 59.18 (OCH_3), 113.64 (C-4a), 120.69 (CN), 127.50 (C=), 128.08 (2C=), 129.26 (2C=), 145.68 (C=), 159.40 (C-2), 163.42 (C-8a), 196.59 (C=O) ppm.

2-Amino-3-cyano-4-(4′-methylphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4j**): mp 211–213°C (lit. [13] 210–213°C); FT-IR (KBr) ν: 3426, 3333, 3224, 2924, 2193, 1677, 1599, 1369, 1035 cm^{-1}. ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 0.91 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.05 (d, $J = 16.1$ Hz, 1H, H-6), 2.21 (d, $J = 16.1$ Hz, 1H, H′-6), 3.57 (s, 2H, CH_2), 4.08 (s, 1H, CH), 6.98 (d, $J =$ 8.1 Hz, 2H, ArH), 7.05 (d, $J = 8.4$ Hz, 2H, ArH) ppm; ^{13}C NMR (d_6-DMSO, 75 MHz), δ: 21.52 (CH_3), 27.66 (CH_3), 29.36 (CH_3), 32.72 (C-7), 36.09 (C-4), 40.12 (C-8), 50.89 (C-6), 59.30 (C-3), 113.77 (C-4a), 120.71 (CN), 128.00 (2C=), 129.80 (2C=), 236.53 (C=), 142.75 (C=), 159.33 (C-2), 163.21 (C-8a), 196.55 (C=O) ppm.

SUPPLEMENTARY INFORMATION

Spectral data of different compounds are available from the corresponding author (e-mail: tlyq@jnu.edu.cn) on request.

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