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An efficient one-pot green synthesis of 4*H*-benzo[*b*]pyrans using guanidinium chloride as polyfunctional organocatalyst

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Abstract

A simple, efficient, and high yielding one-pot protocol has been developed for the synthesis of 4*H*-benzo[*b*]pyrans scaffolds installing a three-component tandem Knoevenagel-cyclocondensation reaction of an aldehyde, malononitrile and dimedone using guanidinium chloride as polyfunctional organocatalyst under solvent-free conditions in high to excellent yields. Various aromatic aldehydes were utilized in the reaction and, in all situations; the desired product was synthesized successfully. The advantageous features of this methodology are operational simplicity, convenient work-up procedures, shorter reaction time and avoiding the use of toxic solvents and purification of products by non-chromatographic methods. The generality and functional tolerance of this convergent and environmentally benign method is demonstrated.

Keywords: Dimedone; 4*H*-benzo[b]pyran; malononitrile; aldehyde; guanidinium chloride.

Introduction

Pyran annulated heterocyle derivatives represent an important class of oxygen-containing heterocycles being the main components of many natural occurring products, and are widely employed as cosmetics, pigments and potential biodegradable agrochemicals and exhibit a wide spectrum of biological activities. 4*H*-benzo[*b*]pyrans are an important class of

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compounds which have received considerable attention in recent years due to their wide range of biological activities [1]. Compounds with these ring systems have diverse pharmacological activities such as anti-coagulant, anticancer, spasmolytic, diuretic, anti-ancaphylactia [2]. Substituted 2-amino-4*H*-pyrans have a special importance among the 6-membered oxygen-containing heterocycles as they have been used as anticancer and antimicrobial agents [3] and photoactive materials [4]. 2-Amino-4*H*-pyran derivatives have been also utilized in the synthesis of blood anticoagulant warfarin [5] and tacrine analogs (cholinesterase inhibitors) [6]. Some catalysts such as silica-bonded *N*-propylpiperazine sodium n-propionate [7], starch solution [8], fructose [9], $Zn_4O(H_2N\text{-}TA)_3$ [10], eggshell [11], silica bonded n-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO) [12], potassium phthalimide-*N*-oxyl [13], inorganic–organic hybrid magnetic nanocatalyst [14], nanoparticles Fe_3O_4 [15], deep eutectic solvents [16], Brønsted acidic hydrogensulfate ionic liquid immobilized SBA-15 [17] and silica-bonded 5-n-propyl-octahydro-pyrimido[1,2-a]azepinium chloride (SB-DBU)Cl [18] have been used for the synthesis of 4*H*-benzo[*b*]pyrans so far. However, most of these methods suffer from some drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious work-up procedures and application of expensive catalysts.

As a part of our research program to develop selective, efficient and green methods and catalysts in organic synthesis [19], we report herein a straightforward one-pot three-component method for the synthesis of 4*H*-benzo[*b*]pyrans in the presence of guanidinium chloride as a polyfunctional organocatalyst under solvent-free conditions.

Experimental

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-400 Avance spectrometers. Chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 mass selective detector. Elemental analyses were carried out by a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the preparation of 4*H*-benzo[b]pyrans 4

A mixture of aromatic aldehyde (1.0 mmol), dimedone (1.0 mmol) and malononitrile (1.0 mmol) was magnetically stirred on a preheated oil bath at 140 °C for 5 min in the presence of guanidinium chloride (0.1 mmol) as catalyst. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and EtOH (5 mL) was added until solid products precipitated. The precipitate was filtered, washed with cold ethanol and dried. The crude product was stirred for 5 min in boiling EtOH and the resulting white precipitate was filtered. The obtained products **4** were found to be pure upon TLC examination.

2-Amino-4-(3,4-dihydroxyphenyl)-7,7-dimet hyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j)

Yield 90 %, mp 241-243 ^{o}C, IR (KBr) (υmax, cm^{-1}): 3464, 3402, 3150, 2199, 1675, 1609, 1262, 1039; ^{1}H NMR (400 MHz, DMSO-d_6); 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.10 (d, 1H, $^{3}J_{HH}$ = 16.0 Hz, CH-8), 2.28 (d, 1H, $^{3}J_{HH}$ = 16.0 Hz, CH-8), 2.42-2.55 (m, 2H, CH-6), 3.98 (s, 1H, CH-4), 6.38-6.63 (m, 4H, Ph-H), 6.93 (br, 2H, NH_2), 8.74 (s, 1H, OH), 8.85 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6); 27.22, 28.99, 32.25, 35.29, 50.53, 59.34, 113.78, 115.13, 115.77, 118.41, 120.45, 136.31, 144.41, 145.40, 158.87, 162.37, 196.18; MS, 326 (M^+, 80), 309 (50), 295 (60), 221 (82), 147 (50), 91 (75), 73 (80), 57 (100); Anal. calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.52; N, 8.58. Found: C, 66.21; H, 5.60; N, 8.64.

2-Amino-4-(2,3-dimethoxyphenyl)-7,7-dime thyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k)

Yield 85 %, mp 218-220 ^{o}C, IR (KBr) (υmax, cm^{-1}): 3459, 3308, 3172, 2183, 1657, 1605, 1368, 1058; ^{1}H NMR (400 MHz, DMSO-d_6); 0.98 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.07 (d, 1H, $^{3}J_{HH}$ = 16.0 Hz, CH-8), 2.25 (d, 1H, $^{3}J_{HH}$ = 16.0 Hz, CH-8), 2.45-2.56 (m, 2H, CH-6), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.55 (s, 1H, CH-4), 6.57-6.98 (m, 4H, Ph-H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6); 27.30, 28.89, 29.85, 32.29, 50.52, 55.97, 58.44, 60.49, 111.43, 113.11, 120.34, 120.59, 124.17, 138.22, 146.50, 152.68, 159.19, 163.30, 196.18. MS, 354 (M^+, 70), 323 (100), 257 (30), 217 (20), 161 (20), 133 (15), 83 (17), 55 (20); Anal. calcd. for $C_{20}H_{22}N_2O_4$: C, 67.79; H, 6.21; N, 7.90. Found: C, 67.85; H, 6.19; N, 7.94.

2-Amino-4-(2-benzyloxyphenyl)-7,7-dimeth yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l)

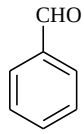
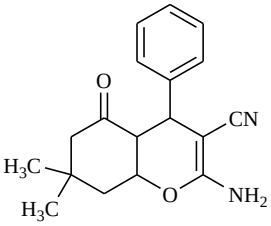
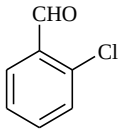
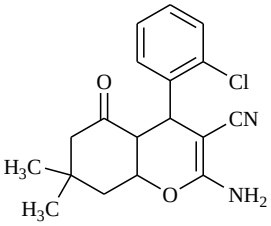
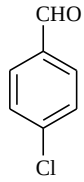
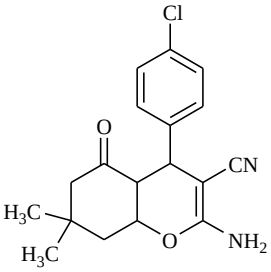
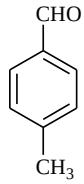
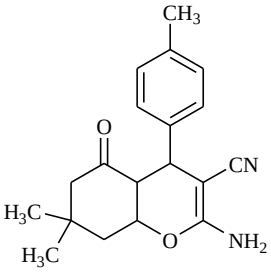
Yield 86 %, mp 258-259 ^{o}C, IR (KBr)

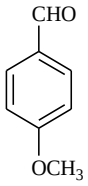
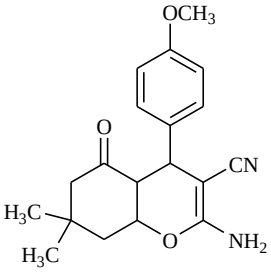
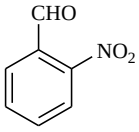
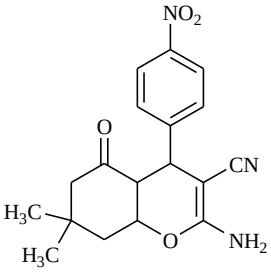
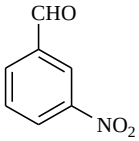
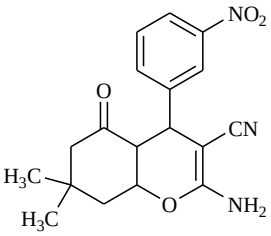
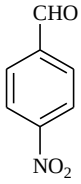
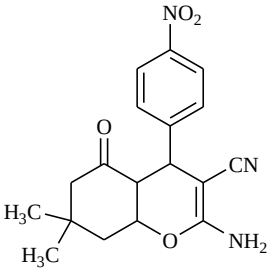
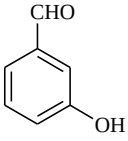
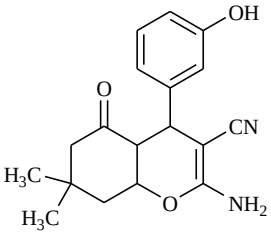
(υmax, cm-1): 3405, 3324, 3208, 2190, 1650, 1596, 1369, 1245; ^{1}H NMR (400 MHz, DMSO-d_6); 0.93 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.05 (d, 1H, $^3J_{HH}$ = 16.0 Hz, CH_2), 2.18-2.24 (m, 2H, CH_2), 2.45 (d, 1H, $^3J_{HH}$ = 17.60 Hz, CH_2), 4.60 (s, 1H, CH), 5.04 (d, 1H, $^3J_{HH}$ = 12.0 Hz, OCH_2), 5.14 (d, 1H, $^3J_{HH}$ = 12.0 Hz, OCH_2), 6.86-7.54 (m, 11H, Ar-CH, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6); 27.40, 28.91, 30.58, 32.12, 50.50, 58.03, 70.14, 112.56, 112.95, 120.42, 121.06, 128.17, 128.22, 128.81, 129.32, 133.05, 137.72, 156.21,159.11, 159.17, 159.21, 163.29, 196.15; MS, 400 (M^+, 10), 383 (15), 309 (95), 292 (10), 260 (20), 243 (10), 227 (60), 182 (10), 131 (10), 91 (100); Anal. calcd. for $C_{25}H_{24}N_2O_3$: C, 75.00; H, 6.00; N, 7.00. Found: C, 75.05; H, 5.94; N, 7.07.

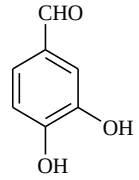
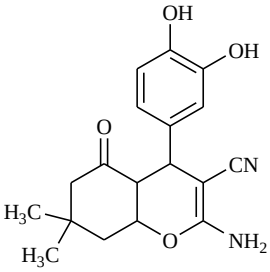
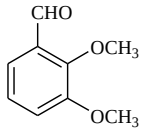
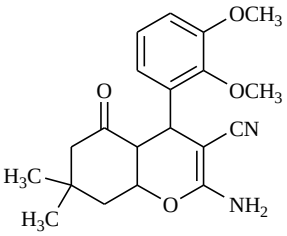
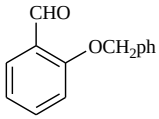
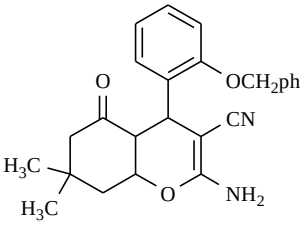
Results and discussion

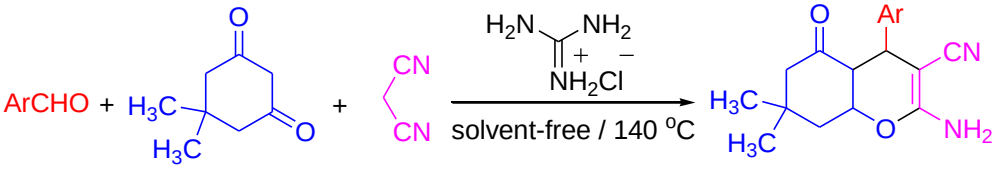
In order to avoid the disadvantages such as volatility and toxicity that many organic solvents inherently have, we employed solvent-free conditions for the synthesis of 4*H*-benzo[*b*]pyrans as a green medium. Initially, the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) was selected as a model reaction in the presence of guanidine hydrochloride as catalyst (10 mol%) under solvent-free conditions. The results showed that no reaction took place at room temperature. To find the optimal reaction conditions, it was examined at 100-160 ^{o}C and the best result was obtained at 140 ^{o}C that was effective in terms of the reaction time and yield. We also varied the amount of catalyst (5, 7, 10, 12, 15 mol%) and the results revealed that 10 mol% gave a high yield of the product. Encouraged by this success, we investigated the use of other aldehydes (benzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 2-nitrobenzaldehyde, 3-nitro benzaldehyde, 4-nitrobenzaldehyde, 3-hydroxybenzaldehyde, 3,4-dihydroxybenzald-ehyde, 2,3-dimethoxybenzaldehyde, 2-benzyloxybenzaldehyde) (**1a-l**), malononitrile and dimedone in this one-pot three component reaction, and obtained a library of 4*H*-benzo[*b*]pyrans **4a-l** (Scheme 1). The results are shown in Table 1.

Table 1. Synthesis of 4*H*-benzo[*b*]pyrans **4** under solvent-free conditions

Entry	Aldehyde	Product	Yield (%)	M.P. (^{o}C)	
				Found	Reported
1		 **4a**	92	230-232	228-230 [20]
2		 **4b**	90	209-211	191-192 [20]
3		 **4c**	93	215-217	207-209 [20]
4		 **4d**	87	220-221	223-225 [22]

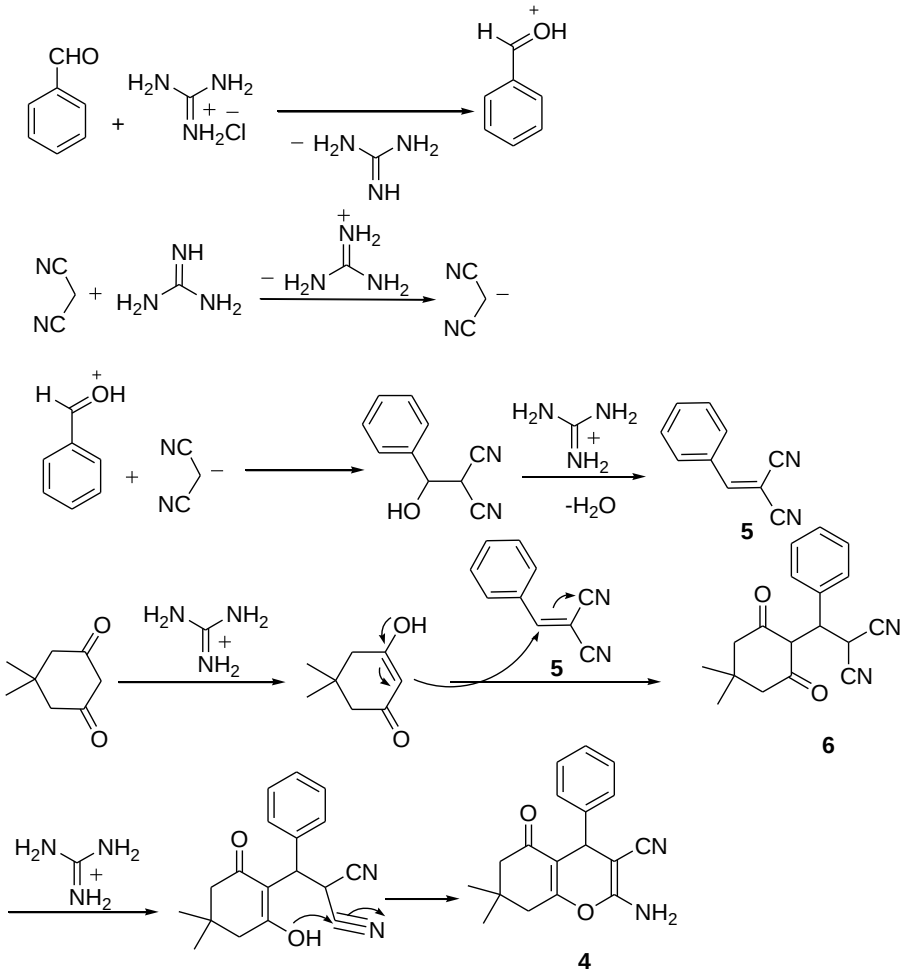
5		 **4e**	88	200-202	198-200 [20]
6		 **4f**	91	238-239	224-226 [6]
7		 **4g**	92	216-217	211-214 [21]
8		 **4h**	89	172-174	177-179 [21]
9		 **4i**	86	235-237	236-238 [22]

10		 **4j**	90	241-243	-
11		 **4k**	85	220-221	-
12		 **4l**	86	258-259	-



Ar = **a**: C_6H_5, **b**: 2-ClC_6H_4, **c**:4-ClC_6H_4, **d**: 4-MeC_6H_4, **e**: 4-$MeOC_6H_4$, **f**: 2-$NO_2C_6H_4$, **g**: 3-$NO_2C_6H_4$, **h**: 4-$NO_2C_6H_4$, **i:** 3-OHC_6H_4, **j**: 3,4-$(OH)_2C_6H_3$, **k**:2,3-$(OMe)_2C_6H_3$, **l**: 2-$phCH_2OC_6H_5$

Scheme 1. One-pot synthesis of 4*H*-benzo[*b*]pyrans **4**



Scheme 2. A proposed mechanism for the synthesis of product **4**

In this reaction, the aromatic aldehydes bearing both electron-donating and electron withdrawing groups reacted with dimedone and malononitrile completely and afforded the corresponding products (**4**). The compounds **4a-i** [7, 10, 20-22] are known products and high to excellent yields were observed for these products (86-93%) compared to the corresponding papers. To the best of our knowledge, the synthesis of compounds **4j-l** has not previously been reported in the literature. The formation of the product in the present reaction is expected to involve the following tandem reaction mechanism. We proposed that guanidine hydrochloride acts as a polyfunctional organocatalyst. The catalyst initially acts as an acid to activate aldehyde. Subsequently, the reaction proceeds through the nucleophilic attack of activated methylene compound **3** (preparation with guanidine hydrochloride as a base) *via*

Knoevenagel condensation to aldehyde which is further dehydration in the presence of hydrochloride of guanidine hydrochloride (as an acid) and intermediate **5** is formed. Then, intermediate **5** can be attacked by dimedone (enol form) *via* a Michael addition to produce intermediate **6**. Finally, the cyano group of intermediate **6** can be attacked by enol form of dimedone in the presence of guanidine hydrochloride, followed by cyclization to afford the product **4** (Scheme 2).

Conclusion

In summary, we have introduced guanidinium chloride that can be used as an efficient polyfunctional organocatalyst for 4*H*-benzo[*b*]pyrans. The current methodology has the advantages of operational simplicity, short reaction times, high to excellent yields and the desired products can be separated directly from the reaction mixture with high purity.

Acknowledgments

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