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Article

An efficient one-pot three-component synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives using starch solution as catalyst

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ABSTRACT

Tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives were synthesized via a one-pot three-component condensation of aromatic aldehydes with malononitrile and dimedone or 4-hydroxycoumarin in excellent yields in the presence of starch solution as a highly efficient homogeneous catalyst. The use of a nontoxic and biodegradable catalyst, simple work-up procedure, and short reaction time are advantages of this method.

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1. Introduction

The development of environmentally benign, efficient, and economical methods for the synthesis of biologically interesting compounds remains a significant challenge in synthetic chemistry [1]. Green chemistry can be recognized as a pioneering approach, which widely reports intrinsic atom economy, energy savings, waste reduction, easy work-ups, and the avoidance of hazardous chemicals [2].

Tetrahydrobenzo[b]pyran derivatives are an important class of heterocyclic compounds having important pharmaceutical and biological activity. These compounds are used as anti-cancer, anticoagulant, diuretic, spasmolytic, and antianaphylactic agents [3]. Therefore, tetrahydrobenzo[b]pyrans have received significant attention from pharmaceutical and organic chemistry communities. Realizing the importance of 4H-pyran derivatives, several synthetic methods have been reported with

the aim of obtaining more biologically potent heterocyclic systems using different catalysts including magnesium oxide [4], silica-bonded 1,4-diazabicyclo[2.2.2]octane [5], silica nanoparticles [6], electro-generated base [7], baker's yeast [8], and amino-functionalized ionic liquid [9]. Other synthetic methods have included the use of microwaves [10], ultrasonic radiation [11], and utilizing additives like hexadecyltrimethylammonium bromide [12], triethylbenzylammonium chloride [13], other alkylammonium salts [14], 4-dodecylbenzenesulfonic acid [15], and (S)-proline [16]. However, limitations of the above methods include poor yields, difficult work-up, and toxic elements. Bandgar and coworkers [17] reported the synthesis of tetrahydrobenzo[b]pyrans in good yield without the use of a catalyst, although prolonged reaction time was required.

Biscoumarins and dihydropyrano[c]chromenes are of considerable interest because they possess a wide range of biological properties [18–24]. A number of methods have been re-

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ported for the synthesis of biscoumarins [25–28]. However, fewer methods have been described for the synthesis of 3,4-dihydropyrano[c]chromenes [29–31]. Some of these procedures require refluxing for hours in organic solvents, use of expensive catalysts, and tedious work-up procedures. In continuing our research based on multicomponent reactions [32–34], herein we report an efficient one-pot three-component synthesis of tetrahydrobenzo[b]pyrans and 3,4-dihydropyrano[c]chromene derivatives using starch solution as a biodegradable catalyst under thermal conditions (Scheme 1).

2. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Infrared (IR) spectra were recorded on a JASCO FT-IR-460 plus spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were obtained with a Bruker DRX-400 Advance spectrometer with using deuterated dimethylsulfoxide (DMSO) and acetone as solvents. All reagents and solvents were obtained from Fluka or Merck and were used without further purification. Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates.

2.1. General procedure for preparation of starch solution

Starch (2 g) was added to water (25 ml) with magnetic stirring at 25 °C. After 30 min, the solution was filtered to remove insoluble starch (amylose) [35]. The filtered solution was used for synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives.

2.2. General procedure for synthesis of tetrahydrobenzo[b]pyran derivatives

A mixture of an aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), and starch solution (4 ml), was stirred at 50 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature (RT), and diluted with water. The mixture was filtered for separation of the product. The crude product was recrystallized from ethanol to afford the pure tetrahydrobenzo[b]pyran derivatives. The desired pure products were characterized by comparison of their

physical data (melting points, IR, and ^1H NMR) with those of known compounds in the literature [13,14].

2.3. General procedure for synthesis of 3,4-dihydropyrano[c]chromene derivatives

A mixture of an aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol), 4-hydroxycoumarin (1.0 mmol), and starch solution (4 ml), was stirred at 50 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with water. The mixture was filtered for separation of the product. The crude product was recrystallized from ethanol to afford the pure 3,4-dihydropyrano[c]chromene derivatives. The desired pure products were characterized by comparison of their physical data (melting points, IR, and ^1H NMR) with those of known compounds in the literature [26,28].

2.4. Spectral data for selected products

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**5a**). IR (KBr, cm^{-1}): 3323, 3395, 3211, 2199, 1680; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.04 (3H, s), 1.13 (3H, s), 2.16 (1H, d, $J = 16.2$ Hz), 2.28 (1H, d, $J = 16.2$ Hz), 2.58 (2H, s), 4.30 (1H, s), 6.25 (2H, br s), 7.17–7.32 (5H, Ar).

2-Amino-4,5-dihydro-4-(phenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (**6a**). IR (KBr, cm^{-1}): 3284, 3377, 3179, 2198, 1708; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.58 (1H, s), 6.70 (2H, br s), 7.26–8.01 (9H, Ar).

3. Results and discussion

To prepare tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives in a more efficient way, and to minimize the reaction time and the amount of catalyst required, the reaction of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), and dimedone (1.0 mmol) or 4-hydroxycoumarin (1.0 mmol) was selected as a model system. The use of different amounts of catalyst (1, 2, 3, 4, and 5 ml) at different temperature was investigated. The best result was obtained with 4 ml of starch solution at 50 °C (Tables 1 and 2).

Using these optimized reaction conditions, the scope and ef-

Scheme 1. Synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives in the presence of starch solution under thermal conditions.

Table 1

Optimization of temperature in synthesis of tetrahydrobenzo[b]pyran derivatives under thermal conditions.

Entry	Temperature (°C)	Isolated yield (%)
1	RT	—
2	10	59
3	20	58
4	30	69
5	40	85
6	50	92
7	60	92
8	70	92

Table 2

Optimization of temperature in synthesis of 3,4-dihydropyrano[c]chromene derivatives under thermal conditions.

Entry	Temperature (°C)	Isolated yield (%)
1	RT	—
2	10	55
3	20	57
4	30	70
5	40	83
6	50	92
7	60	92
8	70	92

efficiency of the reaction were explored for the synthesis of a wide variety of substituted tetrahydrobenzo[b]pyrans and 3,4-dihydropyrano[c]chromene derivatives using aromatic aldehydes, malononitrile, and 1,3-dicarbonyl compounds. The results are summarized in Table 3. The desired pure products were characterized by comparison of their physical data (melting points, IR, and ^1H NMR) with those of known compounds in the literature.

Interestingly, a variety of aryl aldehydes including electron-withdrawing or electron-releasing substituents (*ortho*-, *meta*-, and *para*-substituted) participated well in this reaction and gave the tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives in good to excellent yield. The yields obtained when using aliphatic aldehydes were at trace levels.

Based on literature reports [21,28], we proposed a mechanism for the synthesis of tetrahydrobenzo[b]pyran and 3,4-

Scheme 2. Proposed mechanism for the synthesis of tetrahydrobenzo[b]pyran derivatives in the presence of starch solution as catalyst under thermal conditions.

dihydropyrano[c]chromene derivatives in the presence of starch solution as catalyst (Scheme 2). First, Knoevenagel condensation between **1** and **2** produced 2-benzylidenemalononitrile **3**. Michael addition of **3** with **5** (1,3-dicarbonyl com-

Table 3

Preparation of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives in the presence starch solution as biodegradable catalyst under thermal conditions.

Entry	Ar	1,3-Dicarbonyl	Product	Time (min)	Isolated yield (%)	Melting point (°C)	
						Observed	Reported
1	C ₆ H ₅	3	5a	30	92	230–232	228–230 [15]
2	2-Cl C ₆ H ₄	3	5b	65	82	210–212	208–210 [13]
3	4-Cl C ₆ H ₄	3	5c	45	85	208–210	210–212 [13]
4	2,4-(Cl) ₂ C ₆ H ₃	3	5d	35	94	120–122	115–117 [18]
5	2-NO ₂ C ₆ H ₄	3	5e	40	90	227–230	224–226 [16]
6	3-NO ₂ C ₆ H ₄	3	5f	35	94	210–212	208–210 [20]
7	4-NO ₂ C ₆ H ₄	3	5g	45	85	182–184	183–185 [11]
8	4-Me C ₆ H ₄	3	5h	65	82	210–212	212–215 [20]
9	4-OH-3-OMe C ₆ H ₃	3	5i	40	84	228–230	226–230 [12]
10	4-(Me) ₂ N C ₆ H ₄	3	5j	70	86	220–222	218–220 [19]
11	2,3-OMe C ₆ H ₃	3	5k	35	85	216–218	217–219 [13]
12	4-OH C ₆ H ₄	3	5l	75	83	206–208	204–206 [17]
13	thiophene-2-carbaldehyde	3	5m	40	90	212–214	210–212 [17]
14	2-Furaldehyde	3	5n	35	95	220–222	222–224 [21]
15	C ₆ H ₅	4	6a	25	95	258–260	258–259 [26]
16	3-NO ₂ C ₆ H ₄	4	6b	60	86	260–262	262–264 [26]
17	4-NO ₂ C ₆ H ₄	4	6c	45	95	255–257	258–260 [27]
18	4-Me C ₆ H ₄	4	6e	55	85	253–255	254–256 [28]
19	2-Cl C ₆ H ₄	4	6f	50	82	275–277	273–274 [29]
20	4-Cl C ₆ H ₄	4	6g	35	90	263–265	263–265 [26]
21	2,4-(Cl) ₂ C ₆ H ₃	4	6h	40	87	258–260	261–262 [27]
22	4-OH C ₆ H ₄	4	6i	25	92	260–263	265–266 [26]

pound), followed by cyclization and tautomerization then afforded the corresponding product.

4. Conclusions

We report a novel one-pot three-component synthesis of functionalized tetrahydrobenzo[*b*]pyran and 3,4-dihydropyrano[*c*]chromene derivatives in the presence of starch solution as catalyst. This reaction series was found to be highly effective under thermal conditions. Starch is an effective catalyst and provides a new and useful method for the synthesis of pyran annulated heterocyclic systems by condensation of arylaldehydes, 1,3-dicarbonyl compounds, and malononitrile. The catalyst is environmentally friendly, inexpensive, clean, safe, non-toxic, and easily obtained. Moreover, the procedure offers several advantages including high yields, clean reaction conditions, and no pollution threat to the environment, which together make a useful and attractive process for synthesis of these compounds.

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Graphical Abstract

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