HONEY: A NOVEL, EFFICIENT, AND BIODEGRADABLE CATALYST FOR THE ONE-POT THREE COMPONENT AND GREEN SYNTHESIS OF TETRAHYDROBENZO[B]PYRAN AND 3,4-DIHYDROPYRANO[C]CHROMENES

ABSTRACT

The synthesis of Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives via a one-pot three-component condensation of aromatic aldehydes with malononitrile and dimedone or 4-hydroxycoumarin achieved excellent yields in the presence of honey as a highly efficient homogeneous catalyst. The utilization of a non-toxic and biodegradable catalyst, coupled with high yields, short reaction times, simple work-up, and environmentally friendly conditions, underscores the significant advantages of this method. This approach holds great potential for applications in green pharmaceutical and chemical industries.

Keywords:Green chemistry;Honey;Biodegradable catalyst;Homogeneous synthesis; Three-component synthesis;Tetrahydrobenzo[b]pyran;Dihydropyrano[c]chromene;

Introduction

The development of environmentally benign, efficient, and economical methods for synthesizing biologically interesting compounds remains a significant challenge in synthetic chemistry [1]. Green chemistry stands out as pioneering research, widely recognized for its intrinsic atom economy, energy savings, waste reduction, ease of workup, and avoidance of hazardous chemicals [2]. Catalysts have played a vital role in 20th-century chemistry. As we transition into the 21st century, the push toward clean technology driven by public, legislative, and corporate pressure will present new and exciting opportunities for catalysis and catalytic processes [3]. Chemical clean technology or green chemistry focuses on utilizing methods that reduce or eliminate the use of hazardous substances [4-6].

It is essential to compare this method, with other synthetic approaches in terms of efficiency and process conditions.By evaluating the yields and reaction conditions of this method alongside traditional synthetic routes, such as those utilizing different catalysts or reaction conditions, we can highlight the advantages and limitations of each approach. This comparative analysis can provide valuable insights into the superiority of the honey-catalyzed method and its potential contributions to green chemistry.

The intricate role of honey as a catalyst in chemical reactions remains a subject of ongoing investigation, with several hypotheses and explanations proposed to shed light on its mechanism:Honey is a supersaturated aqueous solution with various sugars, mainly composed of D-fructose and D-glucose (Fig. 1). Moreover, honey contains certain minor constituents such as mineral content, including sodium (Na), potassium (K), magnesium (Mg), and calcium (Ca), hydroxymethylfurfural (HMF), proteins, amino acids, enzymes, vitamins, organic and phenolic acids, flavonoids, carotenoids, volatile substances, and products of the Maillard reaction [7-9].

Carbohydrates, amines, proteins, and minerals present in honey collectively act

as catalysts in diverse chemical reactions. Carbohydrates, functioning as carbon sources, actively engage in carbonyl reactions, notably Cannizzaro reactions, by stimulating carbonyl groups and facilitating intermolecular reactions. Additionally, amines and proteins demonstrate catalytic potential in acid-base reactions, offering active groups crucial for transforming reaction molecules. Moreover, minerals such as iron, manganese, and zinc serve as robust catalysts in oxidation-reduction reactions, enriching honey's catalytic repertoire. This multifaceted nature of honey as a catalyst harnesses the varied properties of its constituents to effectively propel chemical transformations. Carbohydrates, in particular, play a pivotal role as carbon sources, fostering carbonyl reactions by activating carbonyl groups and fostering intermolecular interactions. Amines and proteins in honey act as dynamic agents in acid-base reactions, furnishing active groups that assist in the conversion of reaction molecules. Furthermore, the presence of minerals, like iron, manganese, and zinc, bolsters honey's catalytic prowess, particularly in oxidation-reduction reactions.Additionally, the hydroxyl groups in honey's carbohydrates facilitate the formation of hydrogen bonds with reactant molecules, potentially activating them and streamlining reactions. Certain molecules within honey may also possess unique structures and properties that augment their chemical reactivity, rendering them effective catalysts across various reactions. While these insights provide valuable glimpses into honey's catalytic function, further research is essential to fully unravel the intricacies of its mechanism and exploring its potential applications in organic synthesis and other chemical processes [10-16].

4H-Benzo[b]pyran derivatives are an important class of heterocyclic compounds with significant pharmaceutical and biological activities. These compounds are utilized as anticancer, anticoagulant, diuretic, spasmolytic, and antianaphylactic agents [17a], antibacterial [17b], antimicrobial [17c], antiviral [17d], anti-hypertensive, antiallergic, antifungal, antimalarial, and antiproliferative agents [17e]. Consequently, 4H-benzo[b]pyrans have garnered considerable attention from the pharmaceutical and organic chemistry communities. Recognizing the importance of 4H-pyran derivatives, several synthetic methods have been reported with the aim of producing more biologically potent heterocyclic systems. These methods employ various catalysts such as magnesium oxide [18], SBDABCO [19], silica nanoparticles [20], electrogenerated bases [21], Baker's yeast [22], amino-functionalized ionic liquids [23], as well as other approaches including microwave irradiation [24], ultrasonic radiation [25], and the use of additives such as hexadecyltrimethylammonium bromide (HTMAB) [26], triethylbenzylammonium chloride (TEBA) [27], other alkylammonium salts [28], 4-dodecylbenzenesulfonic acid (DBSA) [29], (S)-proline [30], etc.

Figure 1 Structure of D-fructose and D-glucose

Dihydropyrano[c]chromenes are of considerable interest due to their wide range of biological properties [32-38]. However, fewer methods have been described for the synthesis of these compounds [39-45]. The limitations of the above methods include poor yields, the presence of toxic elements, and the requirement for refluxing for hours in organic solvents, as well as the use of expensive catalysts

and tedious work-up procedures. Continuing our research based on multi-component reactions [46-48], in this study, we report a practical method wherein inexpensive, clean, safe, environmentally friendly, and commercially available honey acts as a bio-resource catalyst for synthesizing Tetrahydrobenzo[b]pyrans and 3,4-Dihydropyrano[c]chromene derivatives using aldehyde, malononitrile, dimedone, or 4-hydroxycoumarine in H2O/EtOH under thermal conditions (Scheme 1).

Scheme 1 Synthesis of Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives in the presence of honey

Experimental

Melting points and IR spectra were measured using an Electrothermal 9100 apparatus and a JASCO FT-IR-460 plus spectrometer, respectively. The 1H NMR spectra were obtained using Bruker DRX-400 Advance instruments with DMSO and acetone as solvents. All reagents and solvents were obtained from Fluka and Merck and used without further purification. TLC was performed on Silica-gel Polygram SILG/UV 254 plates.

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

A mixture of an aldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), and honey (0.4 g) was stirred at 70°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 then filtered, and the resulting precipitate was washed with distilled water to separate the product. The crude product was recrystallized from ethanol to afford pure tetrahydrobenzo[b]pyran derivatives. The desired pure products were characterized by comparing their physical data (melting points, IR, and 1H NMR) with those of known compounds in the literature [27].

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

A mixture of an aldehyde, malononitrile, and 4-hydroxycoumarine (molar ratio: 1:1:1) along with 0.5 g of honey in 5 ml of water-ethanol (4:1) was stirred at 60°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 then filtered, and the resulting precipitate was washed with distilled water to separate the product. The crude product was recrystallized from ethanol to obtain pure 3,4-dihidropyrano[c]chromene derivatives. The desired pure products were characterized by comparing their physical data (melting points, IR, and 1H NMR) with those of known compounds in the literature [40, 42].

2.4 Some spectral data for selected products are represented below

1. *2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile* (5a):

m.p= 225-228 °C, IR (KBr, cm^{-1}): 3323, 3395, 3211, 2199, 1680; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 0.97 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.11 (d, 1H, CH_2), 2.28 (d, 1H, CH_2), 2.52 (s, 2H, CH2), 4.27 (s,1H, CH), 6.75 (s, 2H, NH_2), 7.17-7.32 (m, 5H, Ar-H).

2. *2-Amino-7,7-dimethyl-5-oxo-4-(4-nitrophenyl)-5,6,7,8-tetra hydro-4H-chromene-3-carbonitrile* (5c):

m.p= 176-179 °C, IR (KBr, cm^{-1}): 3509, 3368, 2181, 1680, 1217; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.10 (d, 1H, CH_2), 2.25 (d, 1H, CH_2), 2.50 (s, 2H, CH_2), 4.21 (s, 1H, CH), 6.87 (s, 2H, NH_2), 7.39 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H).

3. *2-Amino-7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-5,6,7,8-tetra hydro-4H-chromene-3-carbonitrile* (5e):

m.p= 206-207 °C, IR (KBr, cm^{-1}): 3444, 3325, 3208, 2171, 1676, 1609, 1507; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 0.91 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.04–2.48 (m, 4H, $2CH_2$), 4.22 (s, 1H, CH), 5.66 (s, 2H, NH_2), 7.08–7.20 (m, 4H, Ar-H).

4. *2-Amino-7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile*(5k):

m.p= 199-201 °C, IR (KBr, cm^{-1}): 3372, 3308, 3212, 2198, 1686, 1598, 1500; 1H NMR (400 MHz, DMSO-d_6): δ (ppm)= 0.99(s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.17

(d, 1H, CH_2), 2.25 (d, 1H, CH_2), 2.48 (s, 2H, CH_2), 3.74 (s, 3H,OMe), 4.21 (s, 1H, CH), 6.81 (d, 2H, Ar-H), 6.94 (s, 2H, NH_2), 7.15 (d, 2H, Ar-H).

5. *2-Amino-4,5-dihydro-4-(phenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile*(6a):

m.p= 170-173℃; IR (KBr, cm^{-1}): 3284, 3377, 3179, 2198, 1708; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 4.58 (s, 1H, CH), 6.70 (s, 2H, NH_2), 7.26-8.01 (m, 9H, Ar-H).

6. *2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile* (6b):

m.p= 265-268 °C; IR (KBr, cm^{-1}): 3476, 2190, 1720, 1612; ^{1}HNMR (400 MHz, DMSO-d_6): δ (ppm)= 3.15 (brs, 2H, NH_2), 4.63(s, 1H, CH), 7.25-8.01 (m, 8H, Ar-H).

7. *2-amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile* (6f):

m.p= 256-260℃; IR (KBr, cm^{-1}): 3460, 3295, 3161, 2190, 1715, 1677, 1590, 1158; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 4.56 (s, 1H, CH), 7.13 (s, 2H, NH_2), 7.38 (d, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 7.48 (t, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.86 (d, 1H, Ar-H).

8. *2-amino-4-(4-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile* (6n):

m.p= 266-267℃; IR (KBr, cm^{-1}): 3359, 3314, 3178, 2196, 1713, 1677, 1612.1171; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)= 4.51 (s, 1H,CH), 6.75 (d, 2H, Ar-H), 7.11 (d, 2H, Ar-H), 7.37 (s, 2H, NH_2), 7.41-7.47 (m, 2H, Ar-H), 7.69 (t, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 9.38 (s, 1H, OH).

Results and discussion

To determine the optimal conditions, the effect of temperature on the reaction rate was initially investigated for the synthesis of tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives via a three-component condensation reaction of 3-Nitrobenzaldehyde, malononitrile, and dimedone (1:1:1) in the presence of 0.5 g of honey in water and ethanol (Table 1). It was observed that the best results were achieved at a temperature of 70°C (Table 1, entry 7). The reaction was completed within 15 minutes, yielding the desired product in 94%

yield.Subsequently, different ratios of water to ethanol solvent were examined. The maximum yield was obtained with a ratio of 3:1 (Table 1, Entry 4). Additionally, the study aimed to determine the optimal catalyst amount. Various amounts of catalyst were tested, with the maximum yield achieved at 0.4 g of catalyst. Further increases in the amount of honey in the reaction did not significantly affect the product yield.

Table 1: Optimization conditions for preparation of tetrahydrobenzo[b]pyrans in the presence of varing amounts of honey, temperature, and solvent

Entry	Temp. (°C)	Solvent (water : ethanol)	Catalyst(g)	Time(min)	Yield(%)[a]
1	25	1:1	0.5	720	Trace
2	50	1:1	0.5	720	42
3	**70**	1:1	0.5	25	89
4	70	**3:1**	0.5	20	91
5	70	1:3	0.5	35	82
6	70	3:1	0.3	25	90
7	70	3:1	**0.4**	15	94

[a] Yields refer to isolated pure product

This review was conducted to investigate the preparation of 3,4-Dihydropyrano[c]chromene derivatives via a three-component condensation reaction of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), and 4-hydroxycoumarin (1.0 mmol) in the presence of 0.5 g of honey in water and ethanol (Table 2). It was found that the optimal conditions for the reaction were a temperature of 60°C (Table 2, entry 5) and the use of 0.5 g of honey with a water-ethanol ratio of 4:1.

Table 2: Optimization conditions for preparation of 3,4-Dihydropyrano[c]chromene in the presence of varying amounts of honey, temperature and solvent

Entry	Temperature(°C)	Solvent (water : ethanol)	Catalyst (g)	Time(min)	Yield(%)[a]
1	r.t	1:1	0.5	720	Trace
2	50	1:1	0.5	40	68
3	**60**	1:1	0.5	17	94
4	70	1:1	0.5	25	91
5	**60**	**4:1**	**0.5**	**20**	**94**
6	60	3:2	0.5	20	91
7	60	1:4	0.5	30	78
8	60	4:1	0.4	25	88
9	60	4:1	0.6	20	92

[a] Yields refer to isolated pure product

Using these optimized reactions, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives using aromatic aldehydes, malononitrile, and dimedone or 4-hydroxycoumarin. The results are summarized in Table 3.

Table 3: Preparation of Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives in the presence of honey as a biodegradable catalyst under thermal condition

Entry	Aldehyde	Substrate	Product	Time (min)	Yield (%)[a]	m.p(°C) Lit. m.p(°C)[Ref]
1			**5a**	17	94	225-228 (226-228) [49]
2			**5b**	15	95	202-203 (201-205) [50]
3			**5c**	13	96	176-179 (178-180) [26]
4			**5d**	15	95	202-204 (200-202) [49]
5			**5e**	15	94	206-207 (207-209) [49]
6			**5f**	15	89	212-215 (210-211) [51]
7			**5g**	15	91	199-201 (197-198) [52]
8			**5h**	15	93	114-116 (115-117) [53]
9			**5i**	12	90	209-212 (208-210) [30]
10			**5j**	22	89	211-212 (209-211) [50]
11			**5k**	30	88	199-201 (197-199) [50]
12			**5l**	40	82	172-173 (170-173) [49]
13			**5m**	28	90	205-208 (206-208) [52]
14			**5n**	40	83	235-237 (238-240) [54]

15	**5o**	35	88	209-213 (210-212) [55]
16	**5p**	15	89	>300 >300 [56]
17	**5q**	35	84	215-217 (214-215) [51]
18	**5r**	30	76	293-294 (295-297) [50]
19	**5s**	55	71	170-173 (172-174) [57]
20	**6a**	25	92	258-260 (257-258) [40]
21	**6b**	23	91	265-268 (266-267) [41]
22	**6c**	20	94	261-262 (261-262) [40]
23	**6d**	20	88	260-261 (260-262)[58]
24	**6e**	20	89	255-258 (255-257) [59]
24	**6f**	20	78	256-260 (261-262) [41]
25	**6g**	22	92	275-276 (274-277) [62]
26	**6h**	17	90	285-288 (289-290) [63]
27	**6i**	25	91	249-252 (250-252) [58]

28	**6j**	30	88	227-230 (228-229) [64]
29	**6k**	30	89	253-255 (254-255) [42]
30	**6l**	35	88	248-250 (247-249) [42]
31	**6m**	50	87	263-266 (264-266) [60]
32	**6n**	33	89	266-269 (266-267) [40]
33	**6o**	45	82	252-253 (253-254) [61]
34	**6p**	42	86	268-269 (266-268) [60]
35	**6q**	20	84	>300 -
36	**6r**	50	82	244-247 [65]

[a] Yields refer to isolated pure product

Interestingly, a variety of aryl aldehydes, including those with electron-withdrawing or electron-releasing substituents (ortho-, meta-, and para-substituted), participated effectively in this reaction and provided Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives in good to excellent yields. However, the yield for aliphatic aldehydes was minimal.

As the bulk of honey is primarily made from sugar, we conducted a test by repeating the reaction with pure sugars in the same amounts present in honey. The reaction time was longer, and the product yield obtained was lower compared to honey. These results suggest that sugars play an important role in the catalytic reaction. However, other factors may also contribute to the reaction, such as

organic acids, amino acids, metals, minerals, vitamins, etc. While we have not established a mechanism for the formation of Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromenes ring systems, a reasonable possibility for this synthesis in the presence of honey as a catalyst is indicated in Scheme 2.

We have demonstrated that hydrogen bonding can form between protons in the free OH groups of the sugar in honey and the substrate, leading to their activation during the reaction [60, 66-69]. According to the literature [33, 40], first, Knoevenagel condensation between 1 and 2 produces 2-benzylidenemalononitrile 3. Subsequent Michael addition of 3 with 5 (dimedone or 4-hydroxycoumarin), followed by cyclization and tautomerization, yields the corresponding product (Scheme 2)[6].

Scheme 2A plausible mechanism for the formation of tetrahydrobenzo[b]pyran in the presence of honey

In addition to its synthetic efficiency, it is crucial to conduct a more comprehensive assessment of the environmental impacts of this method. This assessment should include an analysis of energy consumption, waste generation, and overall environmental footprint compared to conventional synthetic routes. Emphasizing the environmental benefits of green synthetic approaches, such as reduced energy consumption and minimized waste generation, can underscore the importance of sustainable practices in synthetic chemistry.

To fully assess the potential of this method, its efficiency and applicability in synthesizing a broader range of tetrahydrobenzo[b]pyran and 3,4-dihydropyrano[c]chromene derivatives should be evaluated using diverse starting materials. By testing the method with various substrates and functional groups, its versatility and scope can be determined, allowing for a comprehensive understanding of its synthetic utility. This evaluation can highlight the method's potential for application in the synthesis of diverse organic compounds and its relevance in pharmaceutical and chemical industries.

Conclusions

This study introduces an innovative approach to synthesizing Tetrahydrobenzo[b]pyran and 3,4-Dihydropyrano[c]chromene derivatives using honey as a catalyst in a one-pot three-component reaction. The utilization of honey as a catalyst offers numerous advantages, such as high yields, short reaction times, simple work-up procedures, and environmentally friendly conditions, which perfectly align with the principles of green chemistry.

The experimental procedures provide detailed instructions on synthesizing the target compounds, including reaction conditions, catalyst amount, solvent ratios, and characterization techniques. Optimizing reaction parameters demonstrates honey's effectiveness as a catalyst in promoting the desired transformations. Additionally, the role of honey as a catalyst is discussed, suggesting that its various constituents, such as sugars, minerals, amino acids, and organic acids, contribute to the catalytic activity. The proposed mechanism highlights the role of sugars in facilitating the catalytic process, particularly.

The reaction mechanism involves the activation of substrates through hydrogen bonding between the protons of the OH groups in the sugars present in honey and the reactants. This activation facilitates key steps, including Knoevenagel condensation, Michael addition, and cyclization, leading to the formation of the desired products.

Overall, this study presents a promising and environmentally friendly approach for the green synthesis of biologically active heterocyclic compounds using a natural, biodegradable catalyst. Overall, this study presents a promising and environmentally friendly approach for the green synthesis of biologically active heterocyclic compounds using a natural, biodegradable catalyst.

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