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Hibiscus sabdariffa: biocatalyst for solvent-free synthesis of dihydropyrimidinone derivatives

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In vitro studies show Hibiscus Sabdariffa (Sorrel), an ingredient found in many herbal tea blends and other beverages, has natural and biocatalyst properties, and can be easily used as a catalyst in organic transformations. The Hibiscus Sabdariffa can be simply prepared from herbal tea in water and has played the role of solvent cum catalyst for the Biginelli reaction. Dihydropyrimidinone's (DHPMs) are nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance. An efficient and greener synthesis of a series of DHPMs derivatives were accomplished via three-component one-pot cyclocondensation between aromatic aldehydes, *β*-dicarbonyl compound and urea/thiourea under solvent free conditions. This solvent free and eco-friendly approach has several advantages such as being totally pollution free and having shorter time duration with excellent yields.

Keywords: Biocatalyst, Hibiscus sabdariffa, Green chemistry, Dihydropyrimidinone's

INTRODUCTION

Dihydropyrimidinone's (DHPMs) which are nitrogen containing heterocyclic ring have attracted increasing interest owing to their biological and pharmaceutical properties [1, 2]. Thus, synthesis of this heterocyclic nucleus is of the most convenient and popular reaction which gives easy access to this nitrogen heterocyclic compounds are the multi component condensation employing aromatic aldehydes, *β*-dicarbonyl compound and urea under solvent free conditions via Biginelli reaction [3- 5]. In this paper, we describe a new methodology for synthesis of DHPMs using Hibiscus sabdariffa as catalyst. Hibiscus sabdariffa as biocatalyst, due to its acidic nature (pH= 3) has been found to be a suitable replacement for various homogeneous acid catalysts. H. sabdariffa, belonging to the family Malvacea is one of the most common flower plants grown worldwide [6- 8]. More than 300 species of Hibiscus are grown over the world [9]. H. sabdariffa is a subtropical plant species grown in countries such as India, Mexico, and Thailand (fig 1) [10]. Hibiscus Sabdariffa is made from the part of the plant called the calyx, which is the green layer that surrounds the flower petals while they are budding. It has a tart, fruity flavor, and is red in color [11]. The mineral content of H. sabdariffa indicates that the potassium was the most abundant inorganic cation in the calyces and in the seeds of Roselle, followed by Ca in the calyces and P in the seeds [12]. The seeds contain 17.8–21% non-edible oil [13] and 20% protein, and are sometimes used for animal feed [14]. H. sabdariffa is known in different countries by various common names, including roselle (English-speaking countries) [9], karkade (Sudan and other Arab countries) [15, 16], Jamaican sorrel (Latin America) [17, 18], rohzelu (Japanese), patwa or laalambaar (Indian) [19], sour tea (Iran), and bissap (West Africa) [13]. Approximately H. sabdariffa contains 15-30% organic acids, including citric, malic, tartaric acids and Hibiscus sabdariffa contains many chemical constituents including alkaloids, l-ascorbic acid, anisaldehyde, anthocyanin, ß-carotene, ß-sitosterol, citric acid, delphinidin, galactose, gossypetin, hibiscetin, mucopolysaccharide, pectin, protocatechuic acid, polysaccharide, quercetin, and stearic acid [20, 21]. Synthesizing, DHPMs using Hibiscus sabdariffa is also one of the application of green chemistry. The green chemistry programme supports the invention of more environmentally friendly chemical processes which reduce or even eliminate the generation of hazardous substances.

EXPERIMENTAL

General

The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

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Figs. 1. Roselle flowering branch

All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Melting points were determined with an electrothermal 9100 apparatus and are uncorrected. IR spectra were determined as KBr discs on a Shimadzu IR-460 spectrophotometer. NMR spectra were obtained on a Bruker Avance DRX-300 MHz spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 using TMS as internal standard. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. Microwave reactions were carried out in a microwave oven (2500 W power; Micro-Synth, Milestone).

Preparation of aqueous extract of Hibiscus sabdariffa:

Fresh sorrel of the red variety was purchased at a local market. De-cored calyces in water (9:1) were processed at 90°C for 60 min. red material (pulp) was centrifuged using micro centrifuge (REMI RM-12C). The clear portion of the aqueous extract (pH=3) of the hibiscus sabdariffa was used as catalyst for the reactions.

General method for the preparation of dihydropyrimidinone/thiones (DHPMs) derivatives:

The equimolar quantities of an aromatic aldehyde (1 mmol), *β*-dicarbonyl compound, (1 mmol), urea/thiourea (1.5 mmol) and hibiscus sabdariffa (1 ml) was finely mixed together in a test tube at 80°C under solvent-free conditions for an appropriate time. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the decanted solutions washed with water (20 mL), then stirred for 10-15 min to remove the excess of urea/thiourea and filtered. The results are summarized in (Table 1). The crude product was dissolved in hot ethanol, filtered off for removing the unsolved material and the filtrate was cooled to afford the pure product. Its identity was confirmed by IR and NMR and its melting point.

Microwave irradiation method

A 10 ml Pyrex tube was charged with a mixture of aromatic aldehyde (1 mmol), *β*-dicarbonyl compound (1 mmol), urea/thiourea (1.5 mmol), and hibiscus sabdariffa (1 ml). The reaction mixture was subjected to microwave irradiation for a suitable time till the reaction was completed (monitoring by TLC). The solid material washed with water (20 mL), then stirred for 10-15 min to remove the excess of urea and filtered. The precipitate washed and recrystallized from EtOH to give pure crystals of pyrimidinones.

Representative spectral data

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahyd ropyrimidine-5-carboxylate (Table 1, 4a): White powder, FT-IR (KBr, cm^{-1}): 3232, 3109, 3106, 2934, 1715, 1697, 1585, 1438, 1363, 1266, 1080; ^{1}H NMR (400 MHz, DMSO-d_6): δ =2.19 (s, 3H), 3.55 (s, 3H), 5.17 (d, *J*=2.26 Hz, 1H), 7.22-7.33 (m, 5H), 7.77 (s, 1H, NH), 9.11 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): 17.80, 50.74, 53.77, 98.99, 126.13, 127.25, 128.41, 144.64, 148.62, 152.15, 165.80 ppm.

Ethyl-4-(2-hydroxy-3-methoxyphenyl)-6-methyl -2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 1, 4c): White powder, FT-IR (KBr, cm^{-1}): 3367, 3226, 3112, 2976, 2949, 1715, 1688, 1637, 1495, 1227, 1089. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.24 (t, *J*=8.6 Hz, 3H), 2.37 (s, 3H), 3.63 (s, 3H), 4.03 (q, *J* =3.2 Hz, 2H), 5.58 (s, 1H), 5.63 (d, *J* =5.56 Hz, 1H), 6.94-6.98 (m, 3H), 7.60 (s, 1H, NH), 9.18 (d, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 15.01, 19.86, 48.65, 56.47, 61.82, 95.62, 110.52, 112.75, 118.54, 119.42, 121.18, 147.85, 153.02, 157.48, 168.94 ppm.

Ethyl-4-(4-Fluorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine- 5-carboxylate (Table 1, 4f): White powder, FT-IR (KBr, cm^{-1}): 3244, 3118, 2982, 1727, 1700, 1700, 1646, 1465, 1315, 1215, 1089; ^{1}H NMR (400 MHz, DMSO-d_6): δ =1.14 (t, *J*= 7.0 Hz, 3H), 2.41 (s, 3H), 4.04 (q, *J*=7.0 Hz, 2H), 5.21 (d, *J*=5.0 Hz, 1H), 7.21-7.32 (m, 4H), 8.03 (s, 1H, NH), 9.53 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): 14.97, 18.70, 54.16, 60.17, 115.18, 116.48, 129.29, 129.35, 148.48, 159.07, 161.21, 165.70 ppm.

Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrah ydro-5-pyrimidinecarboxylate (Table 1, 4g):

White powder, FT-IR (KBr, cm^{-1}): 3349, 3229, 3115, 2976, 1694, 1637, 1456, 1315, 1227, 1095, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (t, J=7.1, 3H), 2.32 (s, 3H), 4.13 (q, J = 6.4 Hz, 2H), 5.21 (d, J=8.1 Hz, 1H), 7.22-7.37 (m, 5H), 9.66 (d, 1H, NH), 10.23 (s, 1H, NH), ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 11.68, 17.56, 53.87, 59.35, 100.09, 122.35, 123.46, 124.99, 144.52, 145.64, 165.09, 174.87 ppm.

Ethyl-6-methyl-2-oxo-4-(2-thienyl)-1,2,3,4-tetra hydro-5- pyrimidinecarboxylate (Table 1, 4i): FT-IR (KBr, cm^{-1}): 3247, 3118, 2982, 1724, 1697, 1462, 1646, 1315, 1221, 1089. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.05 (t, J = 7.0 Hz, 3H), 2.10 (s, 3H), 4.17 (q, J = 9.32 Hz, 2H), 5.49 (d, J = 3.4 Hz, 1H), 6.98-7.44 (m, 3H), 8.10 (s, 1H, NH), 9.79 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 13.32, 18.24, 49.69, 60.02, 99.98, 127.63, 128.60, 130.47, 148.62, 148.75, 155.07, 162.24 ppm.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (Table 1, 4k): White powder , FT-IR (KBr, cm^{-1}): 3250, 3127, 2976, 1700, 1664, 1647, 1516, 1375, 1230, 1092; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09 (t, 3H, J= 7.0), 2.26 (s, 3H), 3.99 (q, 2H, J=6.9), 5.16 (d, 1H, J=3.2), 7.78-7.25 (m, 4H), 7.78 (d, 1H, J=2.6), 9.26 (d, 1H, J=0.9, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): 14.02, 17.77, 53.41, 59.22, 98.83, 128.34, 131.77, 143.75, 148.67, 151.95, 157.68, 165.17 ppm.

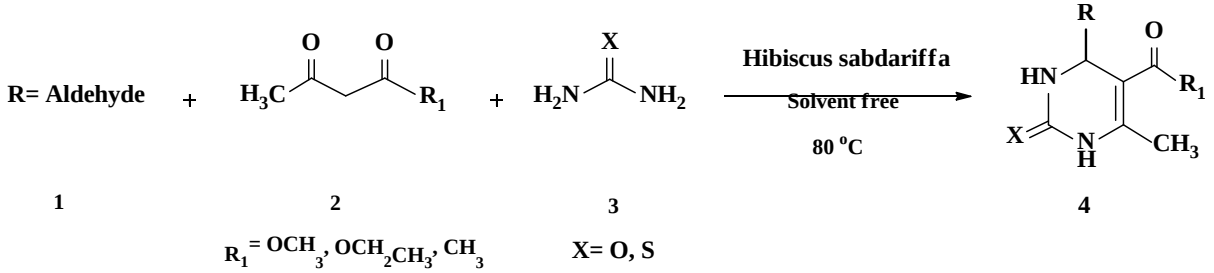
Methyl4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2 ,3,4-tetrahydropyrimidine-5-carboxylate (Table 1, 4m): yellow powder, FT-IR (KBr, cm^{-1}): 3247, 3115, 2982, 1730, 1700, 1649, 1456, 1218, 1089; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3H), 3.62 (s, 3H), 3.85 (s, 3H), 5.28 (d, J =3.2 Hz, 1H), 7.01 (d, J =11 Hz, 2H), 7.26 (d, J =8.4 Hz, 2H), 7.88 (s, 1H, NH), 9.21 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.43, 50.22, 53.65, 56.17, 100.02, 114.30, 129.93, 137.81, 149.03, 153.17, 158.13, 166.03 ppm.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dih ydro-2(1*H*)-pyrimidinone (Table 1, 4p): FT-IR (KBr, cm^{-1}): 3093, 3006, 2925, 1715, 1694, 1582, 1468, 1378, 1287, 1050; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.13 (s, 3H), 2.22 (s, 3H), 3.74 (s, 3H), 5.24 (d, J = 5.2 Hz, 1H), 6.83 (m, 4H), 7.81 (s, 1H, NH), 9.20 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 19.10, 30.03, 52.14, 54.03, 108.84, 119.89, 139.05, 140.27, 145.14, 152.89, 156.16, 195.27 ppm.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydr o-5-pyrimidinyl) ethanone (Table 1, 4q): White powder, FT-IR (KBr, cm^{-1}): 3443, 3295, 2973, 1712, 1670, 1594, 1354, 1098; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.28 (s, 3H), 2.46 (s, 3H), 5.66 (d, J = 11 Hz, 1H), 7.30-7.45 (m, 5H), 10.06 (d, 1H, NH), 10.51 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ = 16.52, 30.46, 52.88, 111.47, 125.02, 127.70, 128.61, 143.34, 145.10, 180.30, 201.05 ppm.

RESULTS AND DISCUSSION

An eco-friendly and economic process for the synthesis of dihydropyrimidinone and thiones (DHPMs) derivatives between substituted aromatic aldehyde, β-dicarbonyl compound, urea/thiourea (Scheme 1) by hibiscus sabdariffa as biocatalyst under solvent free conditions have been synthesized with good yields. As compared to other biocatalyst used under different conditions as depicted in Table 2. As seen from Table 2, as compared to other catalyst, hibiscus sabdariffa is an effective catalyst with high yield and shorter reaction time. To evaluate the feasibility of hibiscus sabdariffa, a modal reaction involving benzaldehyde (1), β-ketoesters (2) and urea/thiourea(3) was carried out at different temperatures under different conditions. In the presence of the catalyst, maximum yield (92%) was observed at 80 ^{o}C with 1 ml of the catalyst. The same reaction was also carried out with 1 ml of catalyst under reflux (ethanol) and microwave conditions, but the yield of the obtained product was lower compared to the reaction under solver-free conditions (Table 3).



Scheme 1. Synthesis of dihydropyrimidinone.

Table 1. Synthesis of different dihydropyrimidinones in presence of hibiscus sabdariffa as a bio catalyst under solvent free and Microwave irradiation conditions

Entry	Aldehyde	R_1	X	[a]Product	Solvent free/MW		m.p (°C)
					Time(min)/Yield(%)		Found Reported[Ref]
1	Benzaldehy	OEt	O	4a	30/92	3/92	201-203 201-203[1]
2	3,5-Dimethyl benzaldehyde	OEt	O	4b	30/88	3/90	205-209 206-208[1]
3	2-Hydroxy-3-methoxy benzaldehyde	OEt	O	4c	30/90	3/94	213-215 216-218[23]
4	2-Phenylpropanal	OEt	O	4d	30/88	3/92	210-212 214-216[23]
5	4-Chloro benzaldehyde	OEt	O	4e	25/90	3/90	218-220 215-217[2]
6	4-Fluoro benzaldehyde	OEt	O	4f	30/94	3/88	194-196 190-192[22]
7	Benzaldehy	OEt	S	4g	25/98	3/90	196-198 208-209[23]
8	2-Chloro benzaldehyde	OEt	O	4h	25/90	3/89	212-214 216-218[26]
9	Thiophene-2-carbaldehyde	OEt	O	4i	25/88	3/92	213-215 213-215[26]
10	3-Nitro benzaldehyde	OMe	O	4j	30/84	3/87	276-278 279-280[25]
11	4-Chloro benzaldehyde	OMe	O	4k	25/86	3/90	202-204 204-207[24]
12	Benzaldehy	OMe	O	4l	25/90	3/92	212-214 209-212[24]
13	4-Methoxy benzaldehyde	OMe	O	4m	30/90	3/96	187-189 192-194[24]
14	Benzaldehyde	OMe	S	4n	15/92	3/88	228-230 228-229[25]
15	2-Hydroxy-3-methoxy benzaldehyde	CH_3	O	4o	30/84	3/94	224-226 225-227[23]
16	4-Methoxy benzaldehyde	CH_3	O	4p	15/94	3/94	162-164 168-170[24]
17	Benzaldehy	CH_3	S	4q	25/92	3/90	229-230 232-233[23]

[a]All reactions were carried out with a molar ratio of aromatic aldehyde, *β*-dicarbonyl compound, urea/thiourea in the presence of hibiscus sabdariffa under solvent-free and Microwave irradiation conditions

[b]Yields refer to isolated pure products..

Table 2. Comparision of hibiscus sabdariffa with reported biocatalysts for the synthesis of dihydropyrimidinones

Catalyst	condition	Time	Yield(%)[Ref]
Tamarind juice	Ultrasound irradiation	3 min	95[1]
Pineapple Juice	Stirring at RT	3.5 hr	82[2]
Lemon Juice	Stirring at RT	2 hr	91[27]

Table 3. Optimizing the reaction conditions

Entry	Hibiscus Sabdariffa (Sour tea) (mL)	Conditions Method/Solvent	Time (min)	Yield (%)
1	-	r.t./Solvent-free	180	-
2	-	80 ^{o}C/Solvent-free	180	-
3	-	Mw./Solvent-free	180	10
4	1	80 ^{o}C/Solvent-free	30	92
5	1	Reflux/ethanol	120	30
6	1	r.t./Solvent-free	120	48
7	1	Mw/Solvent-free	3	90

CONCLUSIONS

We have developed an eco-friendly and economic process for the synthesis of DHPMs by hibiscus sabdariffa as a biocatalyst with good yields under solvent-free and Microwave conditions. The reaction was accompanied having green chemistry approach, shorter reaction time, mild reaction conditions and simple workup procedure.

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