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Natural Organic Acids Promoted Synthesis of 3, 4-Dihydropyrimidin-2(1*H*)-ones/thiones Under Solvent-free Conditions

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Abstract: Naturally occurring organic acids are reported to be highly efficient promoters for the Biginelli reaction under thermal and microwave irradiation using solvent free conditions. Among the various organic acids used, malic acid was found to be the most effective promoter for Biginelli reaction under above reaction conditions. Present protocol is a simple and eco-friendly route for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones/thiones.

Keywords: Biginelli reaction, 3, 4-dihydropyrimidin-2(1*H*)-ones/thiones, naturally occurring acid, green promoters, solvent-free synthesis.

INTRODUCTION

Green or sustainable chemistry has emerged as a major branch of synthetic chemistry in recent years due to the heavy environmental pollution caused by traditional synthetic procedures. This has forced intensive research and detailed investigations in this area leading to the development of many new technologies with greener and relatively cleaner chemical processes [1, 2]. Organic solvents are among the major sources of pollution, due to their large quantity used in reactions. Towards this end, much effort is being devoted to replace toxic and volatile organic solvents with harmless alternatives. Supercritical fluids, ionic liquids, immobilized solvents, fluorous solvents and water have been used in organic synthesis, but their use has its limits. The toxicity of organic solvents and limitations of environmentally benign solvents such as solubility problem of water makes the solvent-free reactions as the most effective approach to perform organic reactions in eco-friendly manner [3,4].

In the past decade, interest in solvent-free reactions has increased immensely due to ecological and economical reasons. Solvent-free methods [5-9] transform traditional procedures into cleaner, safer, and easier to perform. The reduction in energy consumption, reaction time, reactor size and capital investment along with high yields are the advantages of solvent-free processes. Another source of environmental pollution is the use of large amounts of acid catalysts in organic reactions which generates toxic waste that is unsafe to the environment. There is a rising demand for replacing these acid catalysts with cheap, naturally occurring, green acid to change the traditional procedures into the green ones, minimizing chemical waste further. Thus, the use of naturally occurring, green acid catalysts under solvent-free conditions would meet the requirements of modern synthetic chemistry.

A number of organic acids exist plentifully in nature which could be used as green catalysts in synthetic organic transformations. Even though, these acids are nontoxic, biodegradable, readily and cheaply available in nature, they have been used rarely in organic synthesis [10-14].

We have reported citric acid and several other naturally occurring organic acids as highly efficient and eco-friendly promoters for the Beckmann rearrangement and flavones synthesis under solvent-free conditions [16-18]. Pursuing our interest in the development of clean and eco-friendly acid catalysts under solvent-free conditions, here we would like to detail the results of our recent studies about application of naturally occurring organic acids as efficient promoters in the Biginelli reaction. For this purpose, seven naturally occurring organic acids *viz.* citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid were selected (Fig. 1) as green catalysts.

Dihydropyrimidinones (DHPMs) or Biginelli compounds are an important class of medicinal synthones which exhibit a variety of biological activities such as antiviral [19], anti-inflammatory [20], antibacterial [21, 22], anticarcinogenic [23], antihypertensive [24, 25], and calcium channel blockers [26-29]. Furthermore, this structure is also a key component in batzelladine A and B and saxitoxin which are natural marine alkaloids. These molecules are used in the treatment of AIDS as inhibitors for the binding of HIV gp-120 to CD4 cells [30] (Fig. 2).

Biginelli compounds have been used as a precursor in the synthesis of pyrimidine bases [31]. Antihypertensive drugs

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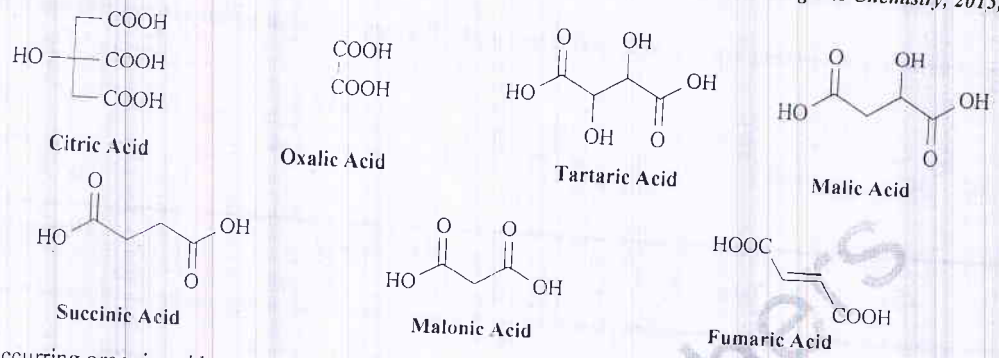

Fig. (1). Naturally occurring organic acids.

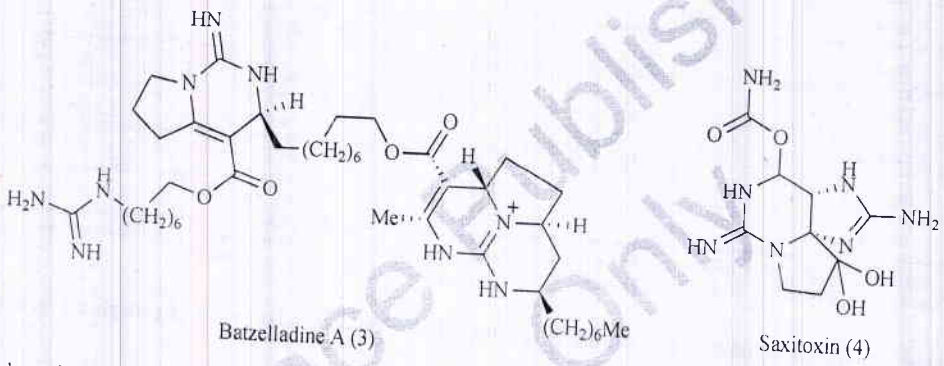

Fig. (2). Marine natural products with 3,4-Dihydropyrimidin-2(1H)-one (DHPMs) core.

such as SQ 32.926, SQ 32.547 were synthesized using Biginelli multi-component reaction [24, 25].

Hydrochloric acid [32], lactic acid [11], citric and tartaric acid [12], ascorbic acid [13], carboxylic acids [14] and *N*-acetyl glycine [15] in solvent have been used in the synthesis of dihydropyrimidinones (DHPMs). However, all the above reported methods suffer from certain drawbacks such as the use of toxic, costly solvents, expensive reagents, co-catalysts, production of considerable amount of byproducts, long reaction time and low yields. Therefore, the development of simple, inexpensive, highly efficient yet eco-friendly catalysts for acid catalyzed organic transformations is worthwhile. We report herein a simple and highly efficient protocol for Biginelli reaction using citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid as green promoters under thermal as well as microwave irradiation using solvent-free conditions.

RESULTS AND DISCUSSION

Screening of naturally occurring organic acid promoters

We started our study with screening the catalysts, for the synthesis of Dihydropyrimidinones (DHPMs). Benzaldehyde **1a,** urea **2** and ethyl acetoacetate **3** were selected for a model reaction. Initially, the mixture of benzaldehyde **1a** (0.5 g, 4.71 mmol.), urea **2** (0.28 g, 4.71 mmol.), ethyl acetoacetate (0.613 g, 4.71 mmol.), and citric acid (4.71 mmol.), was heated either in a preheated oil bath, at 160 °C for 10 min, or in a microwave reactor for 5 min. After the completion of the reaction (TLC check), the reaction mixture was allowed to cool to room temperature, and water (10 mL) was added. The solid obtained on stirring was filtered and washed with water. Crude product was purified by recrystallization using aqueous ethanol to yield Dihydropyrimidinones (DHPMs) **4a** (93% and 94% respectively) (Table **1**, entry 1). All the seven organic acids used were found to be effective promoters of the Biginelli reaction providing Dihydropyrimidinone (DHPMs) **4a** in good to excellent yields (Table **1**). In the above screening study citric, malonic and oxalic acid (Table **1**, entries 1, 4 and 5 respectively) were found to be superior promoters than fumaric, succinic and tartaric acid (Table **1**, entries 2, 6, and 7 respectively), whereas the best results were obtained by using malic acid (Table **1**, entry 3). These results further show under microwave irradiation that the reaction was found to be faster (5 min.) and completed with slightly better yields compared to conventional heating (10 min).

Standardisation of Reaction Condition and Preparation of Compounds 4a-m

Next, the effect of the amount of malic acid on the model Biginelli reaction was investigated. It was found that one mole equivalent of malic acid is essential for the completion of the reaction. However, the use of less than one mole equivalent of the acid resulted in low yield of the product along with the recovery of the starting material even for extended reaction time. In order to check the generality and scope of this protocol, various aromatic aldehydes were subjected to the Biginelli reaction with urea/thiourea and ethyl acetoacetate under the above reaction conditions using malic acid as a promoter at 140 °C. Results indicated that the Biginelli reaction proceeded smoothly under conventional heating within 10 minutes to give the corresponding Dihydropyrimidinones (DHPMs) **4** in good to excellent yields (Table **2**). Microwave irradiation required less time and displayed comparable yields when compared to conventional heating. The synthetic utility of this general reaction protocol was also examined on a larger scale, where benzaldehyde **1a** (5.0

mL) was subjected to the Biginelli reaction under the above reaction conditions using malic acid as the promoter, the corresponding Biginelli compound **4a** was obtained in an excellent yield.

CONCLUSION

To conclude, we report an efficient procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones *via* the Biginelli reaction using naturally occurring organic acids like citric, oxalic, tartaric, malic, succinic, malonic and fumaric acid as an environment-friendly acid promoters under solvent-free conditions. Present protocol allowed us to synthesize a wide variety of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in good yields. It was found that malic acid shows superior reactivity in Biginelli reaction under both conventional as well as microwave irradiation. Furthermore microwave irradiation reduces reaction time and gives comparable yields against conventional heating. This protocol has several advantages over reported methods in terms of the operational simplicity, use of cheaply available acids, eco-friendly and renewable natural promoters, solvent-free reaction conditions, short reaction time, easy work up and high yields. The present protocol is useful in small as well as large scale synthesis of dihydropyrimidinones. Further studies are in progress to expand the scope of this protocol.

EXPERIMENTAL SECTION

Reactions were performed in oven-dried glassware and were monitored by TLC silica gel plates (60 F254) which were visualised by UV and $KMnO_4$ solution. All solvents and reagents were used as obtained from commercial source. Melting points (M.p., uncorrected) were determined in open capillary tubes using paraffin oil bath. All the microwave-assisted reactions were performed in Discover Lab Met microwave system (CEM Corporation, USA) at a specified temperature using the standard mode of operation. Standard ^{1}H NMR and ^{13}C NMR were recorded on a Varian Mercury spectrometer at 300 and 75 MHz respectively in DMSO-d_6 solution and with TMS as an internal standard. IR spectra were recorded on Perkin Elmer Model 1600 series FTIR instrument. Mass spectra were recorded on Agilent 1200SL-6100 LC/MS (ES-API) instrument. All the compounds synthesized are previously reported, physical and spectroscopic data are in agreement with reported values.

General Procedure for Biginelli Reaction

The mixture of aromatic aldehyde **1a** (0.5 g, 4.71 mmol), urea **2** (0.28 g, 4.71 mmol), ethyl acetoacetate **3** (0.613 g, 4.71 mmol) and malic acid (0.631 g, 4.71 mmol) was heated either in a preheated oil bath at 140 °C for 10 min or in microwave reactor for 5 min. After completion of reaction (TLC check), the reaction mixture was allowed to cool at room temperature and water (10 mL) was added. The solid obtained on stirring was filtered and washed with water. Product was purified by recrystallization using aqueous ethanol.

***6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4a** (Table **2**, entry **1**): Mp 202-204 °C (lit. [33] mp 202-204 °C); IR (KBr) ν: 3245, 2979, 1730, 1706, 1650, 1497, 1222, 1091, 704 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.22 (s, 1H), 7.75 (s, 1H), 7.33-7.22 (m, 5H), 5.14 (d, J = 3.4 Hz, 1H), 4.01 (q, J = 6.7 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 6.7 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 165.3, 152.2, 148.3, 144.8, 128.4, 127.3, 126.3, 99.3, 59.2, 53.9, 17.7, 14.0; LCMS (ES-API) m/z: 261.1(M+H)$^+$.

***6-Methyl-2-oxo-4-p-tolyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4b** (Table **2**, entry **2**): Mp 216-217 °C (lit. [33] mp 216-217 °C); IR (KBr) ν: 3245, 2926, 1707, 1650, 1459, 1230, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.43 (s, 1H), 8.24 (s, 1H), 7.53-7.16 (m, 5H), 5.69 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 2.27 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); LCMS (ES-API) m/z: 275.1 (M+H)$^+$.

***4-(4-Methoxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5 carboxylic acid ethyl ester* 4c** (Table **2**, entry **3**): Mp 204-206 °C (lit. [33] mp 204-206 °C); IR (KBr) ν: 3240, 3113, 2951, 2835, 1712, 1649, 1510, 1456, 1224, 1089, 785 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.38 (s, 1H), 7.24 (m, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.92 (s, 1H), 5.33 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 2.32 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 165.7, 159.2, 153.6, 146.1, 136.1, 127.8, 113.9, 101.5, 59.9, 55.2, 55.1, 18.5, 14.1; LCMS (ES-API) m/z: 291.2 (M+H)$^+$.

***4-(4-Fluoro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4d** (Table **2**, entry **4**): Mp 185-186 °C (lit. [39] mp 182-184 °C); IR (KBr) ν : 3348, 3244, 3082, 2980, 1630, 1231, 1015, 768 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.20 (bs, 1H), 7.73 (bs, 1H), 7.09-7.26 (m, 4H), 5.11 (d, J = 3.3 Hz 1H), 3.95 (q, J = 6.7 Hz, 2H), 2.22 (s, 3H), 1.06 (t, J = 6.7 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 165.2, 159.6, 151.9, 148.4, 141.0, 128.2, 114.8, 99.0, 59.1, 53.2, 17.6, 13.9; LCMS (ES-API) m/z: 279.1 (M+H)$^+$.

***4-(4-Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4e** (Table **2**, entry **5**): Mp 217-218 °C (lit. [33] mp 217-218 °C); IR (KBr) ν: 3242, 3117, 2880, 1722, 1645, 1585, 1091, 781 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.25 (s, 1H), 7.77 (s, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.14 (s, 1H), 3.97 (q, J =7.0 Hz, 2H), 2.25 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.1, 151.9, 148.7, 143.7, 131.7, 128.3, 128.1, 98.8, 59.2, 53.4, 17.7, 13.9; LCMS (ES-API) m/z: 295.2 (M+H)$^+$.

***4-(4-Bromo-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4f** (Table **2**, entry **6**): Mp 225-226 °C (lit. [33] mp 225-226 °C); IR (KBr) ν: 3244, 3111, 2949, 1701, 1648, 1419, 1222, 1089, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.27 (s, 1H), 7.84 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 5.40 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.8, 152.5, 149.3, 144.1, 131.9, 129.1, 120.9, 99.4, 59.8, 54.1, 18.2, 14.6; LCMS (ES-API) m/z: 339.0 (M+H)$^+$.

***6-Methyl-4-(4-nitro-phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester* 4g** (Table **2**, entry

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