Lactic, Malic, Tartaric, Citric and Ascorbic Acid as Natural and Green Organocatalysts for Microwave-Induced Solvent-Free Synthesis of Enaminones

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Summary: The enaminone framework is a versatile building block used in organic synthesis. Herein, a series of *β*-enaminones were synthesized in good to excellent yields from the reaction of various aliphatic and aromatic primary amines with 1,3-dicarbonyl compounds using common natural organic acids (lactic, malic, tartaric, citric and ascorbic acid) as green, eco-friendly and efficient catalysts under microwave irradiation and solvent-free conditions.

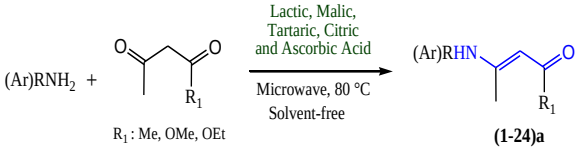
Key word: Natural organocatalysts; Enaminones; Microwave, Solvent-less.

Introduction

β-Amino unsaturated ketones and esters are compounds that their utility in medicinal chemistry as building blocks for novel drug candidates has been widely studied in recent years [1-3]. *β* -Enaminones are significant functionalized building blocks for the synthesis of a diversity of noteworthy biologically active compounds [4-6], which are significant intermediates in the synthesis of pharmaceuticals [7,8], amino acids [9-11], peptides [12],and alkaloids [13]. Several synthetic procedures have been improved for their synthesis, such as cyclization of amino acids, silica-supported perchloric acid, catalyzed by $Zn(ClO_4)_2.6H_2O$, $CeCl_3.7H_2O$, ytterbium(III) triflate and using ionic liquids. In spite of this abundance of methods, these methods may suffer from some disadvantages such as longer reaction times, vigorous reaction conditions, the use of toxic solvents, or unsatisfactory yields that limit mentioned methods to small-scale synthesis. The improvement of straightforward and eco-friendly synthetic procedures for these compounds under benign and green reaction conditions is still noteworthy [14, 35, 36].

On the other hand, there is a gathering requirement for more environmental processes in the chemical industry. This route under the title 'Green Chemistry' requires a change of attitude and a specimen shift from traditional systems of process efficiency, that focus widely on yield of chemicals, to one that allocates economic value to removing waste at source and eschewing the use of perilous and/or toxic meterials [15, 16].

Natural organic acids are broadly current in nature as they can be found in microbial, plant and animal sources. The presence of one or more acidic factors in them makes them link to compounds like esters, amides, and peptides [17].



Scheme-1: Natural organocatalyzed synthesis of *β*-enaminones under solvent- free and microwave conditions.

They are vastly used because they are cheap, nontoxic and safe to handle. Many cases of the use of these catalysts in organic synthesis have been reported in the literature [18, 19]. The naturally occurring organic acids as a class of inexpensive organocatalysts used in this research containing one to three carboxylic functionalities are listed in Fig. 1.

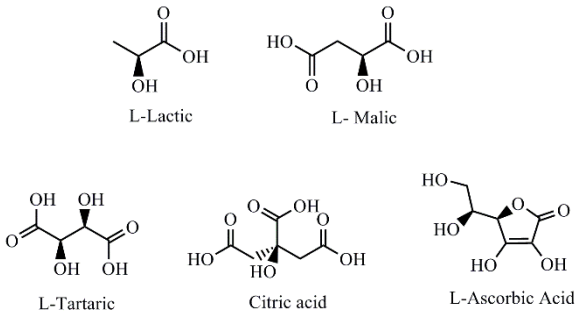


Fig. 1: Common naturally occurring organic acids.

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Experimental

General

Chemicals were purchased from Aldrich and Merck chemical companies and used without further purification. The IR spectra were recorded on a Perkin Elmer FT-IR GX instrument in KBr discs or NaCl plates. ^{1}H and ^{13}CNMR spectra were recorded by a FTNMR BRUKER DRX 500 Avence spectrometer (500 MHz). Chemical shifts were measured in ppm from TMS. $CDCl_3$ was used as solvent as well as the internal standard.

Typical procedure

In a typical experiment, ethyl-3-oxobutanoate (2.0 mmol) and citric acid (2.5 mmole) was ground together in a mortar using pestle for about 30s. Then aniline (2.2 mmol) was added and the mixture was irradiated in a reaction vessel of a Synthwave 402 Prolabo single mode focused microwave reactor for 1.5 min after setting reaction temperature at 80°C and power at 40% (maximum output 300 W). During the reaction the temperature was not allowed to rise above 80°C (by setting the programmer). After completing the reaction (monitored by TLC, n-hexane/chloroform, 3/1), the product was extracted with CH_2Cl_2 (1×15 mL). The organic layer after washing with water was dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum to afford the product **1a** (viscous), that was purified by column chromatography using n-hexane and ethyl acetate (3:1) as an eluent. The solid products were recrystallized from diisopropyl ether as well. All isolated products are known compounds, and their structures were confirmed by melting point and/or identified by comparison of their IR, ^{1}HNMR and ^{13}CNMR spectrometric data with the literature or authentic samples [23-34].

Analytical data for most products

3-Phenylamino- but- 2- enoic acid ethyl ester **(1a):** Oil (Oil) [24], IR (neat, cm^{-1}): 3432, 3014, 2954,1648, 1523, 1289, 1128, 1089, 981, 768; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.22 (t, *J*= 7.3 Hz, 3H), 1.94 (s, 3H), 4.19 (q, *J*= 7.3 Hz, 2H),4.69 (s, 1H), 6.67-7.32 (m, 5H arom.), 11.43 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 16.5 (CH_2CH_3), 19.7 (CH_3), 59.3 (CH_2), 92.5 (=CH), 122.8 (CH), 125.5(CH), 127.6 (CH) , 135.4 (qC), 158 (N-C=), 185.6 (O=C).

3-Benzylamino- but- 2- enoic acid ethyl ester **(2a):** Oil (Oil) [24], IR (neat, cm^{-1}): 3289, 3031, 2954, 1663, 1618, 1511, 1228, 1179, 1150, 1077, 937, 756; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.19 (t, *J*= 7.3 Hz, 3H), 1.92 (s, 3H), 4.18 (q, *J*= 7.3 Hz, 2H), 4.32 (d, *J*= 6.5 Hz, 2H), 4.53 (s, 1H), 7.07-7.30 (m, 5H arom.),11.15 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.8 (CH_2CH_3), 18.1 (CH3), 45.9 ($PhCH_2$), 57.1 (CH_2), 82.5 (=CH), 127.6 (CH), 125.5 (CH), 129.0 (CH), 138.5 (qC), 161.2 (N-C=), 171.2 (O=C).

3-Allylamino- but- 2- enoic acid ethyl ester **(4a):** Oil (Oil) [24], IR (neat, cm^{-1}): 3290, 3065, 2978, 1662, 1616, 1515, 1277, 1161, 1056, 958, 751; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.23 (t, *J*= 7.2 Hz, 3H), 3.66 (s, 3H), 3.82-3.85 (m, 2H), 4.15 (q, *J*= 7.3 Hz, 2H), 4.85 (s, 1H), 5.17-5.28 (m, 2H), 5.81-5.94 (m, 1H), 8.62 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl^{3}$): δ= 14.2 (CH_2CH_3), 24.5 (CH_3), 49.7 (CH_2C=), 61.9 (CH_2CH_3), 82.0 (=CH), 117.8 (=CH_2), 135.0 (=CH-CH_2), 162.1 (N-C=), 171.5 (O=C).

3-Methylamino- but- 2- enoic acid ethyl ester **(5a):** Oil(Oil) [25], IR (neat, cm^{-1}): 3286, 3044, 2981, 1648, 1612,1531, 1275, 1151, 1141, 1096, 948, 799; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.25 (t, *J*= 7.4 Hz, 3H), 1.95 (s, 3H), 2.88 (d, *J*= 7.4 Hz, 3H), 4.10 (q, *J*= 7.4 Hz, 2H), 4.59 (s, 1H), 11.89 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.2 (CH_2CH_3), 18.3 (CH_3), 46.3 (NCH_3), 57.6 (CH_2CH_3), 81.8 (=CH), 161.0 (N-C=), 175.0 (O=C).

3-(1-Phenylethanamino)-but- 2- enoic acid ethyl ester **(6a)**: Oil (Oil) [24], IR (neat, cm^{-1}): 3225, 3019, 2995, 1680, 1615, 1537, 1224, 1183, 1163, 1054, 984, 746; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.22 (s, 3H), 1.38 (t, *J*= 7.2 Hz, 3H), 2.15 (d, *J*= 4.6 Hz, 3H), 4.07 (m, 1H), 4.24 (q, *J*= 7.4 Hz, 2H), 4.65 (s, 1H), 7.15-7.45 (m, 5H arom.), 11.13 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.0 (CH_2CH_3), 18.4 (CH_3), 22.8 (CH_3CH), 56.8 (CH_2CH_3), 61.6 ($CHCH_3$), 82.7 (=CH), 115.9 (CH), 125.9 (CH), 128.1(CH), 129.7(qC), 163.1 (N-C=), 173.2 (O=C).

4-(4-Chloro-phenylamino)-3-penten-2-one **(11a):** m.p. 59-63 °C (61-64) [26]; IR (KBr, cm^{-1}): 3477, 3385, 3202, 3011, 2994, 1622, 1495, 1287, 1182, 1087, 832; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.93 (s, 3H), 2.32 (s, 3H), 3.87 (s,1H), 6.62 (d, 2H arom., *J*= 8.7), 7.11 (d, 2H arom., *J*= 8.8),10.02 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 18.5(CH_3), 23.7 ($COCH_3$), 96.3 (=CH), 123.1 (CH), 124.1 (CH), 125.8 (CH), 135.0 (CH), 135.8 (C-Cl), 141.8 (qC), 158.3 (NC=), 196.5 (O=C).

4-Phenylamino-3-penten-2-one **(12a)**: m.p. 45-48 °C (49-50 °C) [24]; IR (KBr, cm^{-1}): 3436, 3370, 3008, 2994,1653, 1527, 1352, 1322, 1167, 738; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.81 (s, 3H), 2.32 (s, 3H), 3.67 (s, 1H), 6.28-7.06 (m, 5H, arom.), 9.87 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 19.3 (CH_3), 28.7 ($OCCH_3$), 96.6

(=CH), 124.5 (CH), 125.6 (CH), 128.2 (CH), 139.4 (qC), 159.5 (N-C=), 195.7 (O=C).

4-(4-Nitro-phenylamino)-3-penten-2-one **(13a)**: m.p. 137-139 °C (137-139 °C) [26]; IR (KBr, cm^{-1}): 3488, 3368, 3006, 2998, 1667, 1616, 1352, 1281, 1193, 1115, 841, 786; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 2.16 (s, 3H), 2.21 (s, 3H), 4.47 (s, 1H), 7.21 (d, 2H, arom., *J*= 8.6 Hz), 8.21 (d, 2H, arom., *J*= 8.7 Hz), 12.79 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 20.6 (CH_3), 29.6 ($COCH_3$) , 101.2 (=CH), 120.3 (CH), 121.8 (CH), 125.1 (CH), 128.3 (CH), 143.5 (qC), 145.3 (O-C arom.), 157.0 (N-C=), 197.9 (O=C).

4- Benzylamino-3-penten-2-one **(14a):** Oil (Oil) [26], IR (neat,cm^{-1}): 3282, 3046, 2980, 1642, 1608, 1534, 1255, 1141, 1126, 1068, 968, 789; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.82 (s, 3H), 2.05 (s, 3H), 4.35 (d, 2H), 4.96 (s, 1H), 6.82-7.24 (m, 5H, arom.), 11.18 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 18.4 (CH_3), 22.8 ($COCH_3$), 57.9 (CH_2), 80.5 (=CH), 123.6 (CH), 125.2 (CH), 127.6 (CH), 136.4 (qC), 162.3 (N-C=), 191.6(O=C).

4-(p-Tolylamino)-3-penten-2-one **(15a)**: m.p. 64-67 °C (67-68) [21], IR (neat,cm^{-1}): 3283, 3047, 2982, 1644, 1609, 1532, 1254;^{1}H NMR (500MHz, $CDCl_3$): δ= 1.91 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.13 (s, 1H, CH), 6.95 (d, *J*=10.0Hz, 2H, Ph), 7.09 (d, *J*=10.0 Hz, 2H, Ph), 12.38 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ= 19.5 (CH_3), 20.6(CH_3), 28.8 (CH_3), 97.1 (CH), 124.5, 129.4, 135.2, 135.7 (ArC), 160.5 (C-N), 195.5 (C=O).

4-Methylamino-3-penten-2-one **(16a):** m.p. 34-36 °C (31-33 °C) [23]; IR (KBr, cm^{-1}): 3262, 3087, 2981, 1654, 1635, 1567, 1283, 1155, 1065, 973, 789; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.93 (s, 3H), 1.96 (s, 3H), 2.84 (d, *J*= 5.6 Hz, 3H), 11.83 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 18.7 (CH_3), 28. (NCH_3), 29.2 ($OCCH_3$), 94.8 (=CH), 163.2 (N-C=), 192.3 (O=C).

4-(4-Ethyl-phenylamino)-3-penten-2-one **(17a):** m.p. 96-98 °C (95-97 °C) [20], IR (KBr, cm^{-1}): 3485, 3364, 3125, 2995, 1647, 1645, 1496, 1345, 1321; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.67 (s, 3H), 2.01 (q, 2H), 2.09 (s, 3H), 2.37 (t, 3H), 3.45 (s, 1H), 6.95 (d, *J*=10.2Hz, 2H, Ph), 7.09 (d, *J*=10.2 Hz, 2H, Ph), 9.82 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 17.8 ($PhCH_3$), 18.3 ($PhCH_3$), 19.1 (CH_3), 28.6 ($COCH_3$), 98.6 (=CH), 123.7 (CH), 126.5 (CH), 128.3 (CH), 131.8 (CH_3), 131.2 (CH_2), 136.0 (qC), 158.5 (NC=), 197.5 (O=C).

4-(4-Methoxy-phenylamino)-3-penten-2-one **(18a):** m.p. 102-105 °C (106-108°C) [26]; IR (KBr, cm-1): 3484, 3364, 3124, 2991, 1647, 1643, 1496, 1347, 1322, 1127, 855, 767; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.68 (s, 3H), 2.04 (s, 3H), 2.56 (s, 3H), 3.48 (s, 1H), 7.05 (d, 2H arom., *J*= 9.2), 7.12 (d, 2H arom., *J*= 9.0), 9.84 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 17.6 ($PhCH_3$), 18.1 ($PhCH_3$), 19.2 (CH_3), 28.6 ($COCH_3$), 98.7 (=CH), 123.5 (CH), 126.9 (CH), 128.1 (CH), 133.2 (CH_3-C arom.), 136.5 (qC), 158.7 (NC=), 197.3 (O=C).

3-(4-Bromo-phenylamino)- but- 2- enoic acid methyl ester **(21a):** m.p. 121-124 °C (121-123 °C) [25]; IR (KBr, cm^{-1}): 3447, 3336, 3105, 1627, 1584, 1494, 1334, 1257, 1123, 1062, 743; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.98 (t, *J*= 7.2 Hz, 3H), 3.62 (s, 3H), 4.73 (s, 1H, CH), 6.95 (d, *J*= 8.7 Hz, 2H), 7.42 (d, *J*= 8.7 Hz, 2H), 10.34 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 19.8 (CH_3), 51.5 (OCH_3), 84.7 (=CH), 116.4 (C-Br), 133.4 (CH), 137.6 (CH), 137.7 (qC), 160.3 (N-C=), 170.6 (O=C).

3-(Pyrimidin-2-ylamino)but- 2- enoic acid methyl ester **(22a):** m.p. 162-164 °C (161-163 °C) [25], IR (KBr, cm^{-1}): 3325, 3162, 2775, 2686, 1649, 1558, 1579, 1475, 1356, 1223, 802; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.81 (s, 3H), 3.78 (s, 3H), 4.66 (s, 1H), 5.50(br. s, NH), 6.57-6.61 (2H arom., t, *J*= 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 20.38(CH_3), 52.58 (OCH_3), 84.1 (=CH), 111.5 (CH), 157.2 (CH), 158.1 (CH), 139.7 (qC), 185.3 (N-C=), 185.3 (O=C).

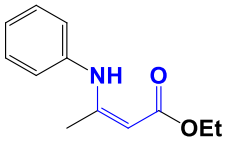
3-(2,4-Dinitrophenylamino)- but- 2- enoic acid methyl ester **(23a):** m.p.162-164 °C (168-172 °C) [23]; IR (KBr, cm^{-1}): 3182, 3011, 2955, 1654, 1622, 1566, 1484, 1261, 1166, 1005, 831; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 2.08 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.62 (s, 1H, vinyl), 8.34-9.12 (m, 3H, arom.), 12.98 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 23.4 (CH_3), 29.7 ($COCH_3$), 97.3 (=CH), 126.1 (CH), 128.7 (CH), 130.8 (CH), 138.4 (qC), 145.6 (qC), 147.5 (qC), 162.3 (N-C=), 197.8 (O=C).

3-(2-Methyl-phenylamino)- but- 2- enoic acid methyl ester **(24a):** m.p. 27-31 °C (26-27 °C) [24] ; IR (KBr, cm^{-1}): 3437, 2692, 1644, 1597, 1439, 1274, 1139, 874, 798; ^1H NMR (500 MHz, $CDCl_3$): δ= 1.32 (s, 3H), 1.84 (s, 3H), 3.48 (s, 3H), 4.67 (s, 1H), 6.77-7.15 (m, 4H arom.), 10.47 (s, 1H,NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.9 (CH_2CH_3), 18.8(CH_3), 51.3 ($PhCH_3$), 84.2 (=CH), 123.1 (CH), 126.3 (CH), 127.1 (CH), 131.3 (CH), 135.5 (qC), 136.2 (CH3-C arom.), 160.7 (N-C=), 170.4 (O=C).

Results and Discussion

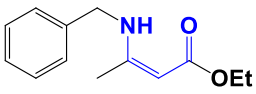
We herein reveal our work on the synthesis of a number of *β*-enamino ketones and esters by inquiring on a wide of naturally organic acids (Table 1) as green and efficient catalysts.

Table-1: The yields and reaction times for MW-mediated solvent-free synthesis of enaminones using organic acids as catalyst, (L= Lactic, M= Malic, T= Tartaric, A= Ascorbic, C= Citric) acid



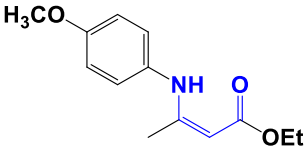
1a

L: 89%, 3 min
M: 91%, 3 min
T: 93%, 1.5 min
A: 84%, 3.5 min
C: 98%, 1.5 min



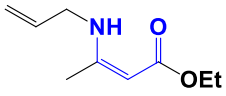
2a

L: 87%, 2.5 min
M: 93%, 3 min
T: 94%, 1 min
A: 87%, 3.5 min
C: 97%, 1 min



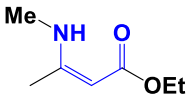
3a

L: 90%, 2.5 min
M: 92%, 2.5 min
T: 94%, 1 min
A: 87%, 3 min
C: 98%, 1 min



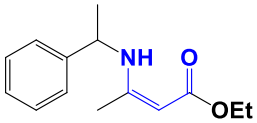
4a

L: 88%, 3 min
M: 93%, 3 min
T: 92%, 1 min
A: 84%, 3 min
C: 93%, 2 min



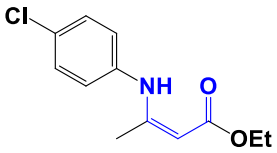
5a

L: 87%, 3.5 min
M: 89%, 3 min
T: 90%, 1.5 min
A: 83%, 3.5 min
C: 92%, 2 min



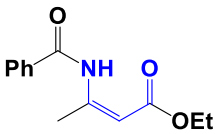
6a

L: 89%, 3 min
M: 92%, 3 min
T: 93%, 2 min
A: 87%, 3 min
C: 93%, 1.5 min



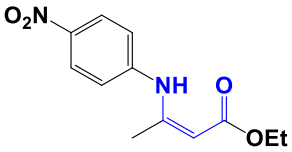
7a

L: 88%, 4 min
M: 89%, 3.5 min
T: 90%, 2 min
A: 84%, 3.5 min
C: 91%, 1 min



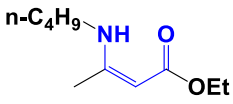
8a

L: 86%, 4.5 min
M: 89%, 4 min
T: 93%, 2.5 min
A: 82%, 4 min
C: 90%, 1 min



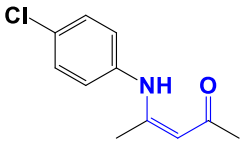
9a

L: 82%, 4.5 min
M: 85%, 3.5 min
T: 90%, 2.5 min
A: 80%, 4 min
C: 90%, 2 min



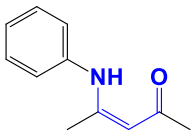
10a

L: 86%, 3.5 min
M: 87%, 3.5 min
T: 90%, 1.5 min
A: 82%, 3.5 min
C: 92%, 1.5 min



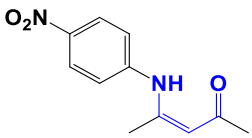
11a

L: 89%, 3.5 min
M: 90%, 3.5 min
T: 91%, 1.5 min
A: 80%, 3.5 min
C: 94%, min



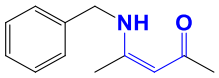
12a

L: 89%, 3 min
M: 90%, 2.5 min
T: 93%, 1.5 min
A: 85%, 3 min
C: 96%, 1 min



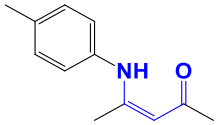
13a

L: 76%, 4.5 min
M: 80%, 4 min
T: 82%, 3.5 min
A: 79%, 4.5 min
C: 89%, 2 min



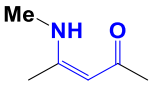
14a

L: 89%, 2.5 min
M: 93%, 1.5 min
T: 93%, 1 min
A: 89%, 3 min
C: 98%, 45 s



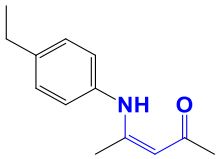
15a

L: 90%, 3 min
M: 92%, 3 min
T: 94%, 1.5 min
A: 88%, 3.5 min
C: 98%, 1 min



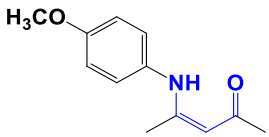
16a

L: 90%, 2.5 min
M: 92%, 2.5 min
T: 94%, 1 min
A: 87%, 3 min
C: 98%, 1 min



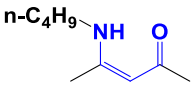
17a

L: 91%, 2.5 min
M: 92%, 2 min
T: 93%, 1 min
A: 87%, 3 min
C: 97%, 45 min



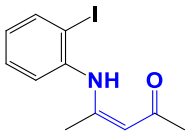
18a

L: 90%, 2 min
M: 92%, 1.5 min
T: 94%, 1 min
A: 89%, 3 min
C: 98%, 30 s



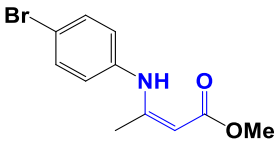
19a

L: 89%, 3.5 min
M: 87%, 3.5 min
T: 91%, 1 min
A: 85%, 3.5 min
C: 96%, 1 min



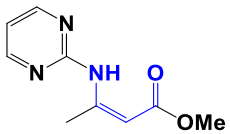
20a

L: 83%, 5 min
M: 86%, 5 min
T: 88%, 3 min
A: 82%, 4 min
C: 91%, 1.5 min



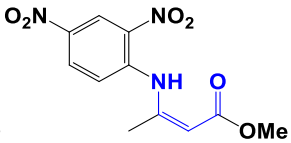
21a

L: 82%, 4 min
M: 83%, 4 min
T: 89%, 2 min
A: 81%, 3 min
C: 92%, 1.5 min



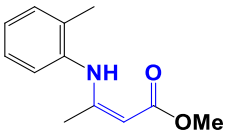
22a

L: 83%, 4 min
M: 84%, 3 min
T: 90%, 1.5 min
A: 80%, 2.5 min
C: 91%, 1 min



23a

L: 74%, 5.5 min
M: 75%, 5 min
T: 81%, 4 min
A: 71%, 6 min
C: 84%, 3.5 min



24a

L: 85%, 3 min
M: 86%, 2.5 min
T: 89%, 2.5 min
A: 84%, 3.5min
C: 90%, 2 min

Reaction conditions: primary amine (2.2 mmol), 1, 3-dicarbonyl compound (2.0 mmol), natural organic acid (2.5 mmol), microwave reaction temperature (80°C)

Among different organic acids applied in this research, citric acid stands the strongest organic acid having the lowest pK_{a1} value (pK_{a1}= 3.13). Consequently, initial screening reaction between ethyl-3-oxobutanoate (2.0 mmol) and aniline (2.2 mmol) was created in the presence of citric acid as the most acidic organocatalyst (**1a**, Table 1). This first catalyzed pattern reaction was performed under solvent-free conditions and microwave heating (80 °C). All synthesized compounds were obtained using this organocatalyzed reaction under the same reaction temperature and solvent-free conditions (Scheme 1 and Table 1).

In addition, to study the effect of amount of catalyst, 1, 1.5, 2, 2.5 and 3 mmol organic acid was applied for this reaction that with 2.5 mmol organic acid obtained the best result (Table 2). Use of higher amount of catalyst neither improves the yield nor the reaction time further. The effect of the microwave reaction temperature in presence of citric acid was also investigated. For this purpose, the same reaction (synthesis of **1a**) was performed at different temperatures under microwave irradiation.

Table-2: The effect of various molar quantities of organic acid catalysts on yields and reaction time for solvent-free synthesis of enaminone **1a** under microwave irradiation (MWI).
(L= Lactic, M= Malic, T= Tartaric, A= Ascorbic, C= Citric) acid

Entry	Catalyst (mmol)	Time (min)					Yield[a] (%)				
		L	M	T	A	C	L	M	T	A	C
1	1	5.5	5.5	5	6	4	67	69	72	54	74
2	1.5	5	4.5	4	5	2.5	70	74	77	65	82
3	2	4	4	2.5	4.5	2	81	86	84	76	90
4	2.5	3	3	1.5	3.5	1.5	89	91	93	84	98
5	3	3.5	3	2	3.5	1.5	88	90	93	82	98

[a] Standard Deviation (STDEV)= L(10.12), M(9.92), T(9.41), A(12.57), C(10.43)

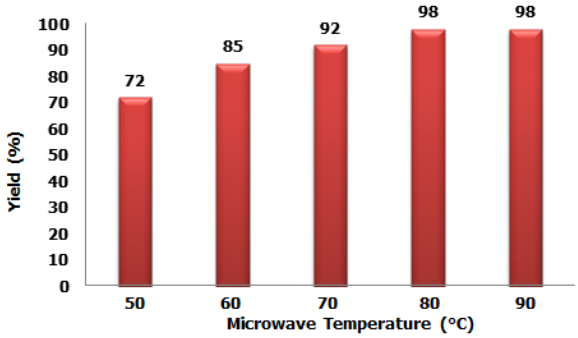
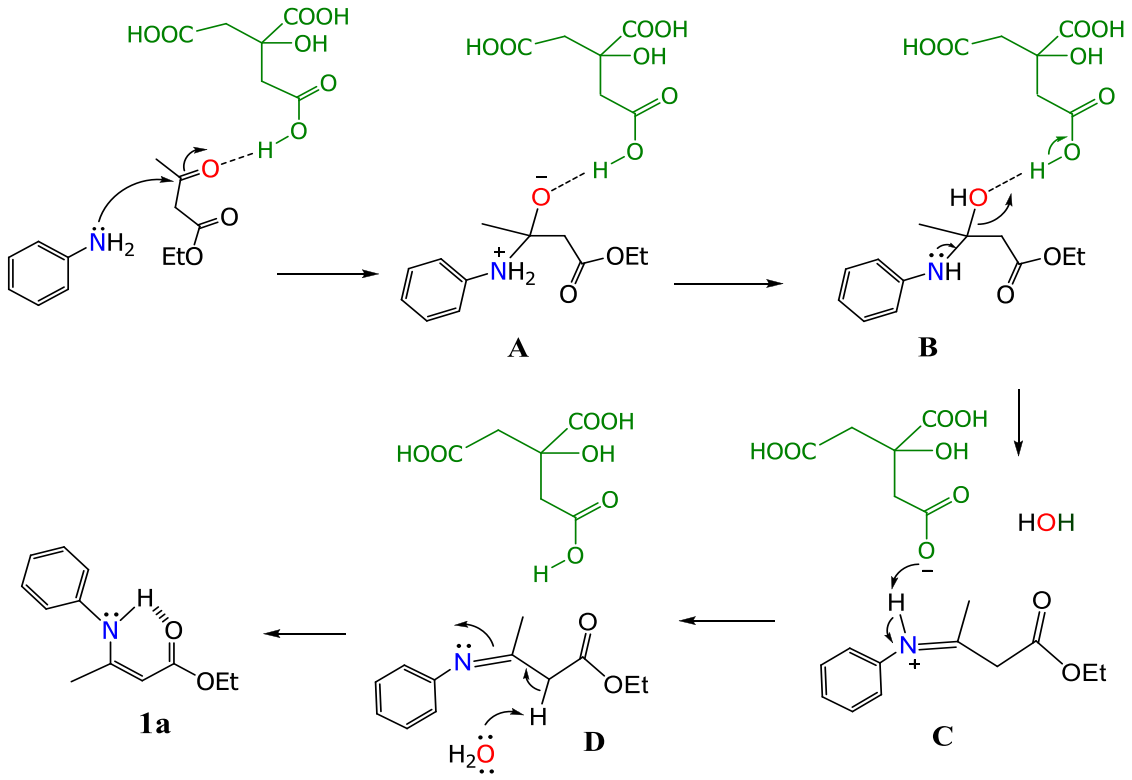


Fig. 2: Effect of microwave reaction temperature in presence of citric acid (2.5 mmol) as catalyst in synthesis of **1a** within 1.5 mi. Standard Deviation (STDEV) = 10.90.

The results revealed that increasing the reaction temperature in the microwave increases the efficiency, so that the best efficiency was obtained at 80 °C. Further raising the microwave temperature did not further improve the reaction efficiency (Fig. 2).

To demonstrate the influence of this procedure, different primary amines including electron-withdrawing groups (such as nitro and chloro groups) and electron-donating groups (such as methyl, aryl and benzyl groups) were treated with 1,3-dicarbonyl compounds to provide the relevant *β*-enaminones in good to excellent yields. This obviously shows that the existence of a an electron-withdrawing group on the benzene ring decreased the reactivity of the substrate to achieve proper efficiency. The plausible mechanism for the citric acid catalyzed solvent- free formation of enaminones was proposed in Scheme 2.

In resumption of steady researches prospecting the utilization of solid acid asserts in the reactivity and synthesis of organic chemicals [21, 22], in this work, the reaction time has been shortened and the synthesis of the products has the feature of prompt reaction, high yield, green, eco-friendly, clean and convenient operation. A comparison of yield of this method with several previously reported methods with solid heterogeneous catalysts for the synthesis of compound **1a** was exhibited in Table 3 as well. Somewhat higher yield was established in this procedure compared to other catalysts.



Scheme-2: The proposed mechanism of citric acid catalyzed solvent- free formation of enaminone **1a.**

Table-3: Effect of various catalysts on MWI solvent-less synthesis of enaminone **1a.**

Entry	Catalyst	Catalyst loading (g, optimized)	Time (min)	Yield[a] (%)
1	SiO_2	0.7	5	85
2	Al_2O_3(acidic)	0.7	8	88
3	Citric acid	0.5	1.5	98
4	K10 clay	0.8	2.5	86
5	KSF clay	0.7	3	91
6	nano-Alumina	0.005	6	85
7	nano-Fe_3O_4	0.006	6	82
8	$ZnCl_2$	0.7	8	81
9	Bentonite	0.8	6	84
10	Kaolinite	0.8	7	80

Reaction conditions: Aniline (2.2 mmol), ethyl-3-oxobutanoate (2.0 mmol), microwave reaction temperature (80°C).
[a] Standard Deviation (STDEV) = 5.33

Finally, to express the superiority of the stated method relative to other reported methods, the yields and reaction time resulted from the pattern compounds in this method were compared with previously reported procedures in the literature (Table 4).

Table-4: Comparison of results for citric acid catalyst with other catalysts for synthesis of enaminone **12a**.

Entry	Catalyst	Condition	Time	Yield[a] (%)	Ref.
1	Silica chloride	solvent-free	5 min	91	[26]
2	$Fe(HSO_4)_3$-SiO_2	solvent free	7 min	89	[29]
3	Silica sulfuric acid	solvent-free	10 min	89	[30]
4	$HClO_4$-SiO_2	solvent-free	14 min	98	[28]
5	Ag nanoparticles	MeOH	8 h	90	[32]
6	Cu nanoparticles	MeOH	2.5 h	92	[33]
7	L-Proline	solvent-free	4 h	85	[31]
8	Citric acid	MWI (80°C)	1 min	96	This work
9	PW/ TiO_2	CH_3CN/ r.t.	10	97	[27]
10	$P2O_5$-SiO_2	solvent-free (80°C)	10	85	[34]

[a] Standard Deviation (STDEV) = 4.61

The presented results exhibit a better catalytic activity of citric acid in the synthesis of enaminone **12a**. Therefore it can be inferred that citric acid (Table 4, entry 8) is the best catalyst as it took only 1 min for completion of reaction with excellent yield of the product. Furthermore only 0.5 g of catalyst is required. This result reveals that citric acid as a natural organic acid is more efficient and more effective compared to other catalysts.

Conclusion

The catalyzed reaction using natural organic acid and microwave irradiation supplies a comprehensive method for the synthesis of *β*-amino-*α, β*- unsaturated esters and ketones. The main utilities of this methodology are faster reaction rates and mild reaction conditions. Natural organic acid catalysts are green, eco-friendly, inexpensive and non-toxic, which makes the procedure more economical, benign and convenient. The remarkable specifications of this method are the high yields of products, solvent-free conditions, availability of the reagents, and cleaner reaction profiles.

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