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Li(Glycine)(CF_3SO_3) as an effective and recoverable catalyst for the preparation of 3,4-dihydropyrimidine-2-(1H)-one under solvent-free conditions

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An efficient solvent-free protocol for the synthesis of 3,4-dihydropyrimidine-2-(1H)-one by the one-pot condensation of aldehyde, ethyl acetoacetate and urea using Li(Glycine)(CF_3SO_3) as a reusable acidic ionic liquid is reported. These reactions have the advantages of this work is clean reaction, simple purification, short reaction time and high yields

Introduction

Ionic liquids (ILs) are synthetic salts that have melting points below 100°C. In these compounds, one or both of the ions are organic species. Delocalized charge of one of ions prevents formation of stable crystal lattice and strong electrostatic forces hold the ions together. The poor coordination of the ions makes these compounds are liquid below 100°C or at room temperature [1]. In recent years, using of ionic liquids in scientific researchs have been surged considerably [2,3]. This growth exactly is associated with their unique properties such as negligible vapor pressure, low toxicity and high thermal and chemical stabilities. For this reason, ILs have been used as organic solvents in applications, such as catalysis and synthesis [4]. Moreover, a series of ILs have proven to be suitable solvents for enzyme reactions [5]. High separation ability, easy operation and zero contamination of the distilled products are other advantages for ILs, and have attractive characteristics for applications in industrial processes and employed as an agent of mass separation azeotropic mixtures or close boiling points mixtures [6,7].

For the synthesis of complex and novel molecular structures, multicomponent reactions (MCRs) are powerful and popular tools [8-11]. This reactions are the major advantages such as shorter reaction time, energy saving, high atom economy and lower cost [12-14]. MCRs provide synthetic access to large compound libraries and do not need deprotection and protection steps. These reactions also are much more environmentally friendly [15-18].

Dihydropyrimidinones (DHPMs) with their unique characteristics such as antibacterial, antioxidant, anti HIV and anticancer have widely spectrum for biological activities [19] and used for synthesis of heterocycle compounds [20]. Previously different derivatives of 3,4-dihydropyrimidine-2-(1H)-one have exhibited calcium channel modulators and neuropeptide Y (NPY) antagonist [21]. In 1893, an Italian chemist, Pietro Biginelli reported a simple and direct reaction for production of DHPMs. This method is based on one-pot

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condensation of an aldehyde, a β-ketoester and a urea that proceed under strongly acidic conditions [22]. But this protocol suffers harsh condition, long reaction time and low yield [23], especially in the case of hetero aromatic aldehydes [24]. Recently, several elegant multicomponent strategies for the synthesis of 3,4-dihydropyrimidine-2-(1H)-one by multi component reactions utilizing catalysts have been reported [25-39]. However some of these methods suffer from disadvantages such as low yield [37], prolonged reaction time [34], use of excess of catalysts [30], use of toxic organic solvents [31] and harsh reaction conditions [27]. Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis.

Experimental

General

All chemical materials were purchased from Fluka and Merck companies and used without further purification. The purity determination of the product and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. The Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Shimadzu Corporation 200-91-527 instrument. The NMR spectra were obtained using a BRUKER DRX-300 AVANCE spectrometer at room temperature in $CDCl_3$ using TMS as an internal standard. Inductively coupled plasma optical emission spectrometry (ICP-OES), measurements were performed on an ICP Varian 735-ES. Raman data were acquired on a Thermo DXR witha 633 nm laser.Thermogravimetric analyses (TGA) were conducted by using a TGA PYRIS 1 thermoanalyzer instrument. Samples were heated from 25 to 600 °C at ramp 10 °C/min under N_2 atmosphere and a TA Instruments DSC 2010 (with a quench cooling accessory, N_2 flow) with 10 °C min^{-1} heating.

Catalyst preparation

Preparation of $Li(CF_3SO_3)$

First, a sample of trifluoromethanesulfonic acid (3 g, 19.2 mmol) was added to 10 mL water in a 20 ml magnetically stirred glass vial. This reaction is exothermic and the acid should be added slowly to the water. The mixture was stirred at 100^{o}C and then LiCl (3 g, 71mmol) was added slowly to the reaction flask. The necessary time for this reaction was estimated to be 1h. After completion of the reaction and formation of the aqueous lithium triflate solution, the residue water was decanted and removed under reduced pressure. The obtained solid metal salt $Li(CF_3SO_3)$ was washed with ethylacetate (2×20 ml) and dried under nitrogen at 120 ^{o}C for one day. The product was found to be pure and no further purification was necessary (2.8g, 93.3% yield). Atomic absorption analysis of this solid metal salt has shown that it is 0.03 mol% in concentration of dissolved Li^+ ion.

Preparation of $Li(Glycine)(CF_3SO_3)$

A mixture of (2.5g, 16.02 mmol) $Li(CF_3SO_3)$, (2.5g, 33.3 mmol) glycine and dry ethanol (10 mL) was taken in a vessel and then heated to 80^{o}C for 15 min. After 15 min of stirring, additional mixing was irradiated in a BANDELIN Sonoplus HD 3200 ultrasonic apparatus at 80^{o}C for 5 min. After formation of the product, reaction solvent was removed under vacuum condition and then remaining ionic liquid in the reaction flaskwas washed with dichloromethane and dried at 60°C under vacuum to give $Li(Glycine)(CF_3SO_3)$ (yield >99%).

General procedure for preparation of 3,4-dihydropyrimidine-2-(1H)-one derivative

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (2 mmol)and $Li(Glycine)(CF_3SO_3)$ (10 mol%) was sealed and stirred at 80 ^{o}C under solvent-free conditions. After completion of the reaction, as indicated by precipitation of solid products from the liquid reaction mixture and TLC experiments, the reaction mixture was diluted with ethanol (10 ml) and stirred for 5 min. The solid catalyst was successfully recovered after evaporation of water under reduced pressure which can be reused. The product was found

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to be pure and no further purification was necessary.

Spectral data of the products

3,4-Dihydro-5-etoxycarbonyl-4-(4-phenyl)-6-methyl-pyrimidine-2(1H)-one (4a): Whitepowder; mp 203-205 °C (lit. 202-203 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J*= 7.6 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3),4.06 (q, *J*= 7.6 Hz, 2H, CH_2), 5.25(s, 1H, CH), 6.29 (s, 1H, NH), 7.28-7.59(m, 5H, H-Aro), 9.66 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.7, 18.3, 55.2, 61.6, 100.8, 127.5, 128.3, 129.9, 144.1, 145.2, 152.3, 166.5.

3,4-Dihydro-5-etoxycarbonyl-4-(2-chlorophenyl)-6-methyl-pyrimidine-2(1H)-one (4b): Whitepowder; mp 216-219 °C (lit. 215-218°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (t, *J*= 7.2 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3),3.97 (q, *J*= 6.8 Hz, 2H, CH_2), 5.22(s, 1H, CH), 5.80 (s, 1H, NH), 6.91-7.14(m, 4H, H-Aro), 9.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 17.3, 54.3, 60.7, 100.6, 112.8, 122.1, 127.5, 129.1, 131.8, 151.3, 155.9, 158.0, 166.4.

3,4-Dihydro-5-etoxycarbonyl-4-(3-chlorophenyl)-6-methyl-pyrimidine-2(1H)-one (4c): Whitepowder; mp 193-195 °C (lit. 192-193°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, *J*= 7.2 Hz, 3H, CH_3), 2.38 (s, 3H, CH_3),4.03 (q, *J*= 7.6 Hz, 2H, CH_2), 5.20(d, *J*= 2.8 Hz, 1H, CH), 6.83-7.02(m, 4H, H-Aro), 7.84 (s, 1H, NH),9.42 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.9, 18.2, 54.3, 61.4, 100.8, 113.3, 113.8, 121.8, 131.5, 147.2, 149.4, 154.0, 161.6, 167.5.

3,4-Dihydro-5-etoxycarbonyl-4-(4-chlorophenyl)-6-methyl-pyrimidine-2(1H)-one (4d): Whitepowder; mp 211-213 °C (lit. 212-214°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, *J*= 8.0 Hz, 3H, CH_3), 2.24(s, 3H, CH_3), 3.92 (q, *J*= 8.0 Hz, 2H, CH_2), 5.09 (d, *J*= 2.8 Hz, 1H, CH), 6.29 (s, 1H, NH), 6.88 (d, *J*= 8.0 Hz, 2H, H-Aro), 7.18 (d, *J*= 8.0 Hz, 2H, H-Aro), 9.76 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ 15.4, 18.5, 53.1, 60.1, 100.9, 122.9, 123.7, 125.8, 142.4, 150.3, 153.9, 167.4.

3,4-Dihydro-5-etoxycarbonyl-4-(3-bromophenyl)-6-methyl-pyrimidine- 2(1H)-one (4e): White powder; mp 185-187 °C (lit. 185-186 °C).IR (KBr, cm^{-1}): *υ* 3200, 3100, 2920, 1690, 1590, 1450. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 1.10 (t, *J*= 6.4 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.98-4.05 (m, 2H, CH_2), 5.21 (d, *J*= 2.8 Hz, 1H, CH), 5.59 (s, 1H, NH), 6.79-6.82 (m, 2H, H Aro), 7.07-7.10 (m, 2H, H-Aro), 9.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 14.4, 15.9, 54.5, 61.0, 99.3, 120.9, 125.0, 129.5, 131.5, 131.8, 145.5, 146.0, 162.5, 165.1.

3,4-Dihydro-5-etoxycarbonyl-4-(2,4-dichlorophenyl)-6-methyl-pyrimidine-2(1H)-one (4f): Whitepowder; mp 249-251 °C (lit. 251–252 °C). IR (KBr, cm^{-1}): υ 3160, 3000, 2980, 1785, 1660, 1425. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (t, *J*= 6.8 Hz, 3H,CH_3), 2.20 (s, 3H, CH_3), 4.10 (q, *J*= 6.8 Hz, 2H, CH_2), 5.36 (s, 1H, CH),5.59 (s, 1H, NH), 7.37–7.56 (m, 3H, H-Aro), 8.70 (s, 1H, NH) .^{13}C NMR (100 MHz, DMSO-d_6): δ 15.5, 18.7, 55.7, 60.0, 95.7, 128.5, 129.2, 130.1, 133.3, 134.0, 150.0, 156.1, 161.0, 165.8.

3,4-Dihydro-5-etoxycarbonyl-4-(3,4-dichlorophenyl)-6-methyl-pyrimidine-2(1H)-one (4g): Whitepowder; mp 223-225 °C (lit. 222-223°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 (t, *J*= 8.0 Hz, 3H, CH_3), 2.30(s, 3H, CH_3), 3.91 (q, *J*= 8.0 Hz, 2H, CH_2), 5.08 (d, *J*= 2.4 Hz, 1H, CH), 6.82-6.98 (m, 3H, H-Aro), 7.94 (s, 1H, NH), 9.14 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ 14.9, 18.2, 54.3, 61.4, 100.8, 113.3, 113.8, 121.8, 131.5, 147.2, 149.4, 154.0, 161.6, 167.5.

3,4-Dihydro-5-etoxycarbonyl-4-(4-fluorophenyl)-6-methyl-pyrimidine-2(1H)-one (4h): Whitepowder; mp 178-180 °C (lit. 175-177°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, *J*= 6.8 Hz, 3H, CH_3), 2.27(s, 3H, CH_3), 4.03 (q, *J*= 8.0 Hz, 2H, CH_2), 5.23 (d, *J*= 2.8 Hz, 1H, CH), 7.10 (d, *J*= 8.0 Hz, 2H, H-Aro), 7.20 (d, *J*= 8.0 Hz, 2H, H-Aro), 7.84 (s, 1H,

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NH), 9.25 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 19.8, 54.3, 60.0, 100.5, 115.5, 129.4, 148.9, 156.2, 161.0, 162.1, 166.8.

3,4-Dihydro-5-etoxycarbonyl-4-(2-nitrophenyl)-6-methyl-pyrimidine-2(1H)-one (4i): Whitepowder; mp 218-220 °C (lit. 220-222°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (t, *J*= 7.2 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3),3.92 (q, *J*= 8.0Hz, 2H, CH_2), 5.51(s, 1H, CH), 6.90-7.30(m, 4H, H-Aro), 7.82 (s, 1H, NH), 9.17 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 17.3, 55.6, 60.8, 100.5, 112.9, 122.1, 130.7, 132.9, 134.9, 151.4, 155.8, 161.4, 166.4.

3,4-Dihydro-5-etoxycarbonyl-4-(3-nitrophenyl)-6-methyl-pyrimidine-2(1H)-one (4j): Whitepowder; mp 225-227 °C (lit. 226-228°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J*= 8.0 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3),4.04 (q, *J*= 8.0 Hz, 2H, CH_2), 5.17(d, *J*= 2.8 Hz, 1H, CH), 6.83-7.26(m, 4H, H-Aro), 7.85 (s, 1H, NH), 9.22(s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.4, 17.9, 52.8, 59.4, 100.6, 113.7, 121.8, 132.5, 142.4, 149.4, 149.9, 154.0, 161.6, 166.4.

3,4-Dihydro-5-etoxycarbonyl-4-(4-nitrophenyl)-6-methyl-pyrimidine-2(1H)-one (4k): Whitepowder; mp 211-213 °C (lit. 208-211°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, *J*= 8.0 Hz, 3H, CH_3), 2.30(s, 3H, CH_3), 4.05 (q, *J*= 8.0 Hz, 2H, CH_2), 5.35 (d, *J*= 2.8 Hz, 1H, CH), 7.36 (d, *J*= 7.2 Hz, 2H, H-Aro), 7.93 (s, 1H, NH), 8.23 (d, *J*= 7.6 Hz, 2H, H-Aro), 9.37 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ 14.9, 19.3, 55.2, 61.4, 100.5, 123.8, 124.7, 126.9, 142.6, 150.8, 154.9, 166.8.

3,4-Dihydro-5-etoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4l): Whitepowder; mp 258-260 °C (lit. 259-260°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (t, *J*= 7.6 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3),3.84(s, 3H,OCH_3), 3.87(q, *J*= 6.8 Hz, 2H, CH_2), 5.49(s, 1H, CH), 6.30 (s, 1H, NH),6.90-7.31(m, 4H, H-Aro),9.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.9, 18.7, 43.6, 56.9, 59.4, 95.8, 112.3, 122.7, 129.7, 129.9, 131.8, 149.9, 151.8, 157.7, 166.8.

3,4-Dihydro-5-etoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4m): Whitepowder; mp 208-210 °C (lit. 207-208°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, *J*= 8.0 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3),3.91(s, 3H,OCH_3), 4.06 (q, *J*= 7.6 Hz, 2H, CH_2), 5.21(d, *J*= 2.8 Hz, 1H, CH), 6.82-7.17 (m, 4H, H-Aro), 7.30 (s, 1H, NH), 9.52 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 19.5, 50.3, 50.7, 60.8, 100.9, 113.7, 113.9, 121.0, 139.9, 143.0, 147.0, 153.9, 161.6, 167.5.

3,4-Dihydro-5-etoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4n): Whitepowder; mp 203-205 °C (lit. 203-204°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, *J*= 7.2 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3),2.90(s, 3H,OCH_3), 3.46 (q, *J*= 7.6 Hz, 2H, CH_2), 5.12(s, 1H, CH), 6.91 (d, *J*= 6.8 Hz, 2H, H-Aro),7.19 (d, *J*= 6.8 Hz, 2H, H-Aro), 7.76 (s, 1H, NH), 9.12 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 18.8, 56.5, 57.8, 66.8, 100.6, 114.7, 127.6, 138.6, 148.2, 154.8, 158.8, 166.9.

3,4-Dihydro-5-etoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4o): Whitepowder; mp 176-178 °C (lit. 174-176°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J*= 6.8 Hz, 3H, CH_3), 2.30-2.31 (m, 6H, CH_3, OCH_3),2.43 (s, 3H,OCH_3),4.05 (q, *J*= 7.6 Hz, 2H, CH_2), 5.26(d, *J*= 2.8 Hz, 1H, CH), 6.97-7.15 (m, 3H, H-Aro), 7.89 (s, 1H, NH), 9.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.8, 21.0, 50.8, 56.3, 56.8,60.6, 100.6, 122.7, 128.9, 130.9, 136.8, 139.7, 144.9, 150.9, 154.4, 166.8.

3,4-Dihydro-5-etoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4p): Whitepowder; mp 177-179 °C (lit. 173-175°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3),3.55 (s, 3H, CH_3),3.76 (s, 3H, CH_3),3.99 (q, *J*= 8.0 Hz, 2H, CH_2), 5.06(d, *J*= 2.8 Hz, 1H, CH), 6.73-6.86 (m, 3H, H-Aro), 7.82 (s, 1H, NH), 8.22 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.2, 18.9, 51.8, 56.8, 60.8, 100.3, 121.7, 128.9, 132.9, 136.7, 139.9, 144.9, 150.9, 152.1, 166.7.

3,4-Dihydro-5-etoxycarbonyl-4-(4-trifluoromethylphenyl)-6-methyl-pyrimidine-2(1H)-one (4q): Whitepowder; mp 177-179 °C (lit. 173-175 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (t, *J*= 7.6 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3),3.89 (q, *J*= 7.6 Hz, 2H, CH_2), 5.52(d, *J*= 2.8 Hz, 1H, CH), 7.27 (d, *J*=

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7.6 Hz, 2H, H-Aro),7.47 (d, *J*= 7.6 Hz, 2H, H-Aro), 7.58 (s, 1H, NH), 9.39 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.2, 18.9, 54.1, 60.1, 99.7, 118.0, 122.3, 129.2, 132.1, 144.1, 147.1, 152.9, 165.8.

3,4-Dihydro-5-etoxycarbonyl-4-(2-hydroxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4r): Whitepowder; mp 198-200 °C (lit. 199-201°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 (t, *J*= 7.6 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3),4.07 (q, *J*= 7.6 Hz, 2H, CH_2), 5.55(s, 1H, CH), 6.91-7.15 (m, 4H, H-Aro), 7.58(s, 1H, NH), 9.35 (s, 1H, NH), 9.75 (s, 1H, OH).^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 17.4, 55.8, 60.6, 100.6, 112.9, 121.8, 129.5, 131.7, 133.3, 151.9, 156.9, 159.0, 167.4.

3,4-Dihydro-5-etoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-pyrimidine-2(1H)-one (4s): Whitepowder; mp 229-231 °C (lit. 231-233°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J*= 7.6 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3),4.02 (q, *J*= 7.6 Hz, 2H, CH_2), 5.09(s, 1H, CH), 6.83 (d, *J*= 7.6 Hz, 2H, H-Aro), 7.11 (d, *J*= 7.6 Hz, 2H, H-Aro), 7.85 (s, 1H, NH),9.52 (s, 1H, NH), 9.74 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.7, 18.3, 54.4, 60.3, 100.8, 115.5, 129.1, 138.3, 148.3, 153.9, 156.0, 166.7.

3,4-Dihydro-5-etoxycarbonyl-4-(4-p-tolyl)-6-methyl-pyrimidine-2(1H)-one (4t): Whitepowder; mp 215-216 °C (lit. 216–217 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, *J*= 7.6 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3),2.30 (s, 3H, CH_3), 4.07 (m, 2H, CH_2), 5.33(s, 1H, CH), 6.29 (s, 1H, NH), 6.87(d, *J*= 8.0 Hz, 2H, H-Aro), 7.17 (d, *J*= 7.6 Hz, 2H, H-Aro), 8.74 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 18.8, 22.8, 56.6, 66.7, 100.2, 115.0, 127.1, 138.7, 149.3, 155.4, 158.5, 166.3.

3,4-Dihydro-5-etoxycarbonyl-4-(4-styryl)-6-methyl-pyrimidine-2(1H)-one (4u): Whitepowder; mp 227-229 °C (lit. 234-236°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J*= 7.6 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3),3.96 (q, *J*= 7.6 Hz, 2H, CH_2), 5.05(d, *J*= 2.8 Hz, 1H, CH), 7.20-7.39 (m, 7H, H-Aro), 7.38 (s, 1H, NH),9.28 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.0, 20.6, 54.3, 61.1, 100.1, 112.8,112.9, 113.9, 126.91, 126.95, 134.3, 148.7, 154.7, 160.1, 163.8, 166.8.

3,4-Dihydro-5-etoxycarbonyl-4-(2-furyl)-6-methyl-pyrimidine-2(1H)-one (4v): Whitepowder; mp 204-206 °C (lit. 205-207°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, *J*= 8.0 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3),4.07 (q, *J*= 8.0 Hz, 2H, CH_2), 5.20(d, *J*= 2.8 Hz, 1H, CH), 6.18 (d, *J*= 2.8 Hz, 1H, CH), 6.25 (s, 1H, CH), 7.11 (s, 1H, CH), 7.41 (s, 1H, NH),9.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 19.5, 44.4, 60.6, 98.4, 106.5, 113.7, 138.4, 150.9, 153.9, 156.8, 167.5.

Results and discussion

Catalyst characterization

ICP analysis of Li(CF_3SO_3)

Inductively coupled plasma optical emission spectrometry (ICP-OES) to show insertion of the Li^+ to the trifluoromethanesulfonic acid(CF_3SO_3H) was used. This analysisindicates the leachable portion of the elements in (Table 1). This method proves that Lithium has been intercalated into Glycine spaces.

Table 1. ICP analysis with ME-01 Elements Method.

Element	DL [a]	Leachable Portion
Li	1	33700

[a] DL: Detection Limit (in ppm).

IR analysis of Catalyst

Fig. 1. presents the FT-IR spectra of Glycine, CF_3SO_3H, Li(CF_3SO_3) and Li(Glycine)(CF_3SO_3). In the spectrum of starting CF_3SO_3H characteristic absorption bands at 1072 cm^{-1} was assigned to the stretching vibrations of the (S=O) group. Also, appearing bands at 699 $cm^{-1}$and 955cm^{-1} to be assigned to the symmetric and asymmetric (S-O) group. The spectrum shows a relatively broad band in the range of 3000 to 3600 cm^{-1} which indicates the presence of SO_3H group. In the case of Li(CF_3SO_3), the peaks at about 655 cm^{-1} and 925 cm^{-1} are due to the Li^+ ion which is associated with a decrease in the υ (S-O) vibration mode. Also, appearing band in 1077cm^{-1}correspond to the S=O stretching vibrations. Absenting band around 3000 to 3600 cm^{-1} can be attributed to the replacement of the hydrogen atom by the Li^+ ion on the (S-O) group. From these data can be inferred that the novel ionic liquid has been

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confirmed.Significant point in the spectrum of glycineis the presence of COO^- band at 1645 cm^{-1} and NH bands in the range between 3100-3600 cm^{-1} which contributed to identification of the ionic liquid. The IR spectra of ionic liquid Li(Glycine)(CF_3SO_3) refer to the successful formation of this compound. All bands ranging from bands of the glycine and CF_3SO_3 have been appeared in their place. In this spectra, the band of COO^- in comparison with the glycine spectra is drawn to the lower absorption and implies that the lithium atom is also attached to the COO^- group.

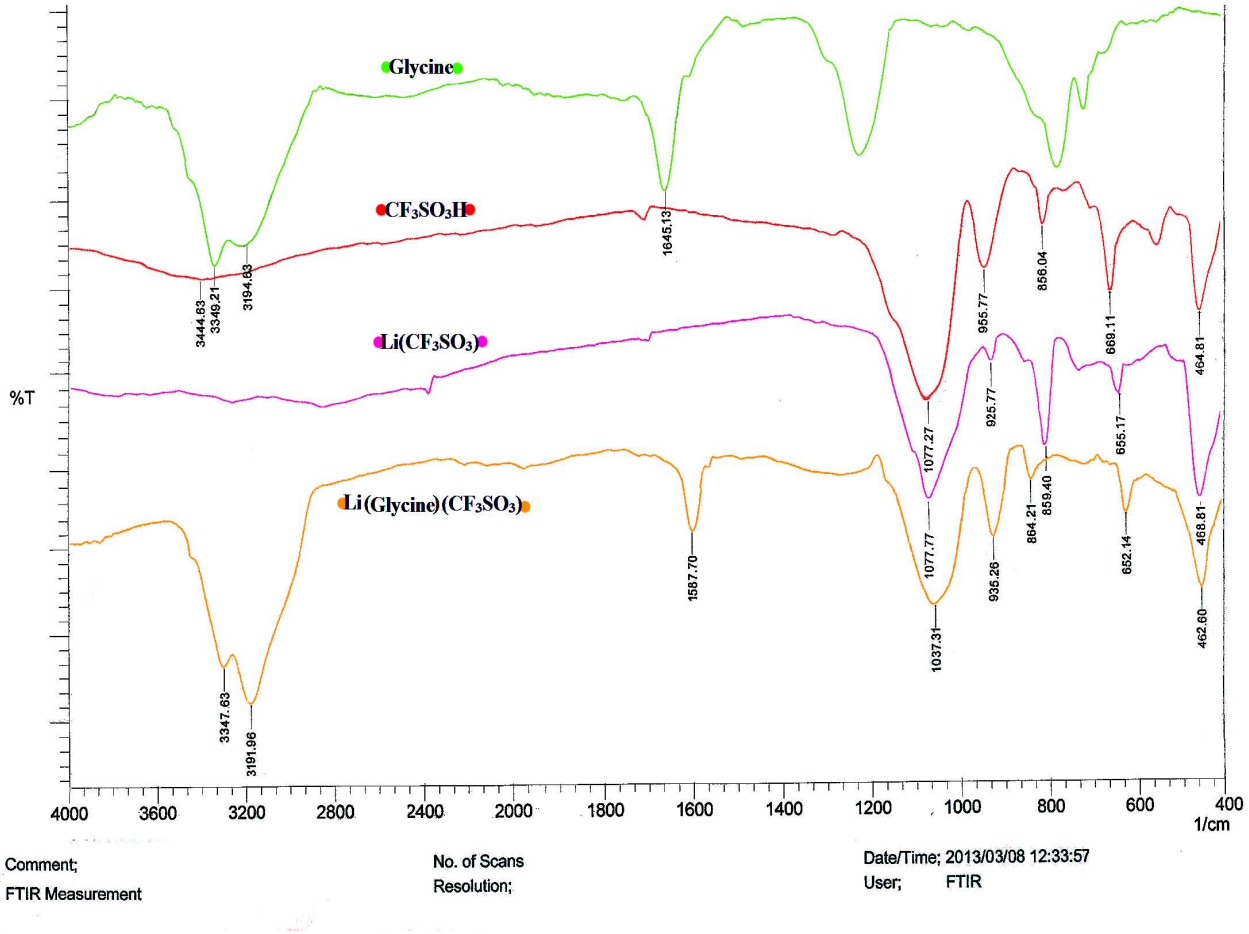

Fig.1. FT-IR spectra of Li(Glycine)(CF_3SO_3)

Thermal Studies of Li(Glycine)(CF_3SO_3)

The stability of Li(Glycine)(CF_3SO_3) was determined by using thermo gravimetric analysis (TGA) coupled with differential scanning calorimetry (DSC) and the results are summarized in Fig. 2. The catalyst was heated from room temperature to 300 ºC but no change was observed in the mass. In the case of glycine, the lack of change in mass goes up to 250 ºC and then starts to evaporate. According to these observations, we reach to two general conclusions about this ionic liquid. The first achieved result is that glycine is coordinated to Li^+. The second result tell us that $Li(CF_3SO_3)_3$ and glycine is not simply mixed together in solvent.Due to the DSC curve that was performed using a liquid N_2 quench cooling accessory, a T_g at around -73 ^oC can be seen which refers to an amorphous glass reforming a liquid upon heating [40].

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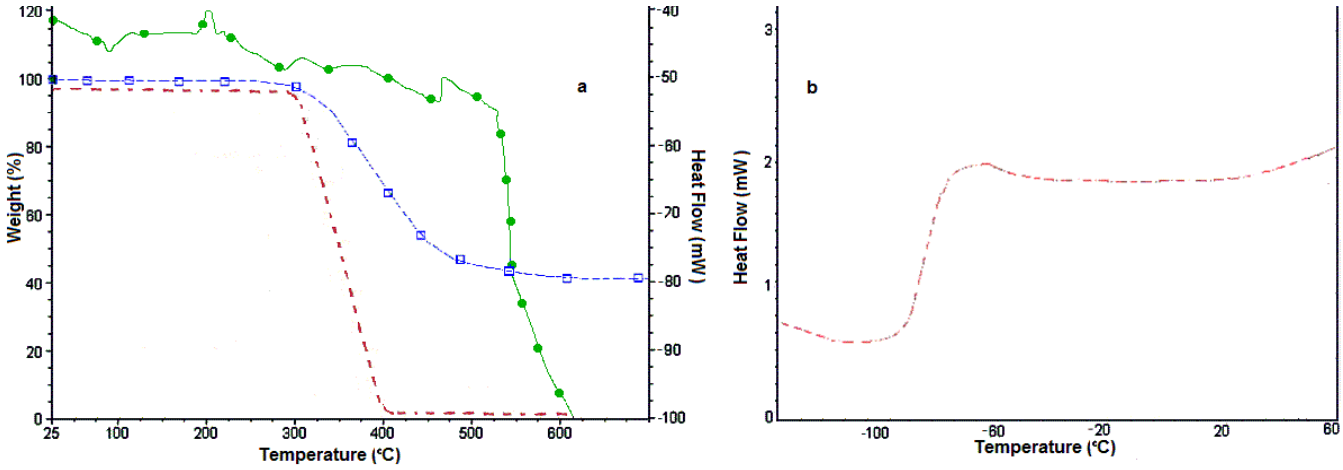

Fig.2.(a) Photograph of Li(Glycine)(CF_3SO_3) (inset) and TGA-DSC of Li(Glycine)(CF_3SO_3), (b) DSC of Li(Glycine)(CF_3SO_3)with liquid N_2 quench cooling.

Raman analysis of Li(Glycine)(CF_3SO_3)

Raman spectroscopy is very suitable for the identification of the molecular structure. This type of spectroscopy is used to evaluate the geometry and molecular symmetry, to determine the rotational and vibrational frequencies of molecules. According to this specification, we decided to use of this spectroscopy to demonstration of the novel ionic liquid. Raman spectra (633 nm laser) of glycine, Li(Glycine)(CF_3SO_3) and Li(CF_3SO_3) are presented in Fig. 3. Raman bands of CF_3 and SO_3 in Li(CF_3SO_3) appeared in the ranges 790 and 1105 cm^{-1} respectively and showed that a red shift has occurred than Li(Glycine)(CF_3SO_3). This is compatible with displacement of $CF_3SO_3^-$ by glycine around the Li centers. The point that is interestingly and also was observed in the raman spectra is appearance of a peak in the range of 290 cm^{-1} which refers to preferential coordination through the oxygen groups of glycine to the lithium group. The results are shown in Fig. 3.

Atomic absorption analysis of Li(Glycine)(CF_3SO_3)

Atomic absorption analysis of this liquid has shown that it is 0.03 mol% in concentration of dissolved Li^+ ion.

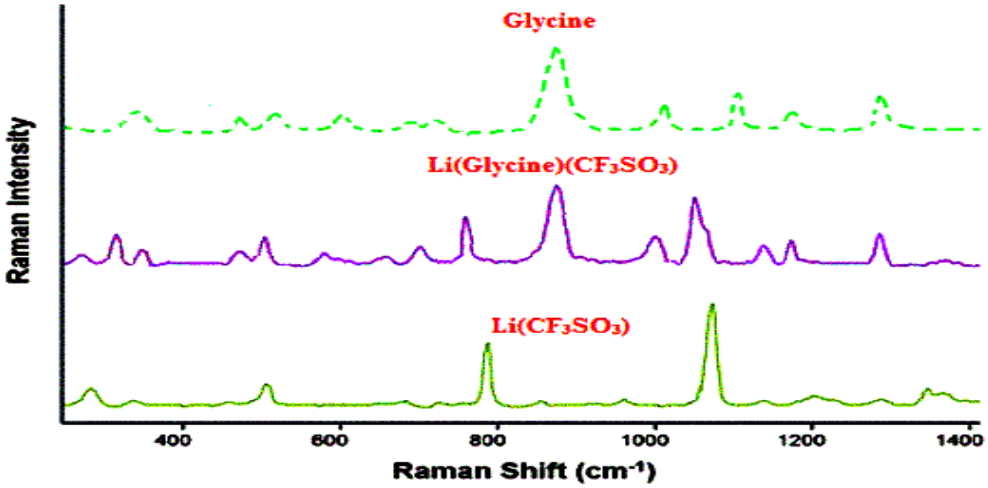

Fig. 3. Raman spectra (633 nm laser) of Glycine, Li(Glycine)(CF_3SO_3), and Li(CF_3SO_3).

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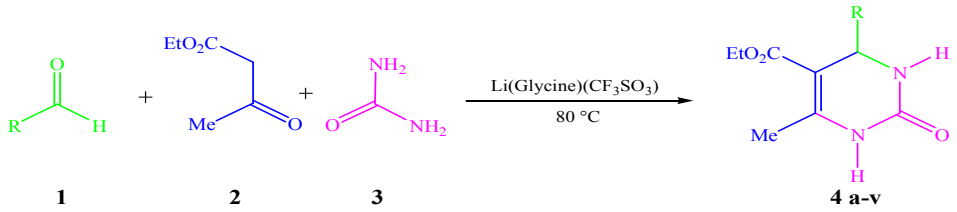
In continuation of our studies on the synthesis of various bioactive compounds [41], we decided to investigate the synthesis of 3,4-dihydropyrimidine-2-(1H)-one derivatives in the presence of Li(Glycine)(CF_3SO_3) as a novel catalyst under solvent-free conditions. The reported route is an appropriate, efficacious and novel method for condensation of aldehyde, ethyl acetoacetate and urea in the presence of Li(Glycine)(CF_3SO_3) as an acidic ionic liquid (Scheme 1).



1 2 3 4 a-v

Scheme 1. One-pot three-component reaction of different aldehydes, ethyl acetoacetate and urea catalyzed by Li(Glycine)(CF_3SO_3) ionic liquid.

First, the optimization of the reaction temperature and the amount of the catalyst required for the reaction of aldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (2 mmol) was standardized by carrying out the reaction in the presence of different amount of Li(Glycine)(CF_3SO_3) at different temperature ranging 25°C to 90°C for different periods of time by conventional heating (Table 2). The obtained results show that below 10 mol% of Li(Glycine)(CF_3SO_3), the yield of product was low (Table2, entry 4), however, increasing in the amount of catalyst had no effect on the yield and only reaction time was prolonged (Table2, entry 10). Also, increasing or decreasing in temperature of the reaction have a reverse effect on the compound yield. Only at 60°C and with 20 minutes of reaction time, the highest product yield of 83% was observed (Table 2, entry 7). With consideration to Table 1, the reaction using 10 mol% of catalyst at 80°C proceeded in highest yield (Table2, entry 8). Monitoring by TLC has shown detectable progress of the reaction for the acidic ionic liquids such as [HMIm]HSO_4 and [BMIm]HSO_4, but these ionic liquids were not as effective as Li(Glycine)(CF_3SO_3). The model reaction gave low yield in even long time when it was run in the ionic liquid [BMIm]BF_4. Adding 20 mol% of the *p*-TSA to the [BMIm]BF_4 lead to increasing the catalytic activity and rate of the reaction (Table 2, entry 3). Interestingly, when the trial reaction was performed in the absence of the novel IL under same reaction condition, nearly no product detected even after 3h (Table 2, entry 11), demonstrating, the catalytic role of Li(Glycine)(CF_3SO_3) in the synthesis of desired 3,4-dihydropyrimidine-2-(1H)-one derivatives.

Table 2. Influence of different catalysts on the reaction of aldehyde, ethyl acetoacetate and urea to afford 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one.[a]

Entry	Ionic liquid (mol%)	Temperature (°C)	Reaction time (min)	Yield (%) [b]
1	[BMIm] HSO_4	80	120	81
2	[BMIm] BF_4	80	200	30
3	[BMIm] BF_4 / *p*-TSA	80	25	60

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4	Li(Glycine)(CF_3SO_3) (5)	80	30	55
5	Li(Glycine)(CF_3SO_3) (10)	25	50	65
6	Li(Glycine)(CF_3SO_3) (10)	40	35	72
7	Li(Glycine)(CF_3SO_3) (10)	60	20	83
8	Li(Glycine)(CF_3SO_3) (10)	80	4	96
9	Li(Glycine)(CF_3SO_3) (10)	90	25	75
10	Li(Glycine)(CF_3SO_3) (15)	80	20	95
11	---------	80	3h	Trace

[a] Reaction conditions: a mixture of 2-chlorobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (2 mmol).[b] Isolated yield.

To improve the yields further and to make the process green, the reaction was run in different solvents (Table 3). It was found that the highest yield (85%) was achieved when the reaction was conducted in PEG as a co-solvent (Table 3, entry 3). Unfortunately, the use of co-solvents system such as DMF, DMSO, CH_2Cl_2, $CHCl_3$and toluene resulted in poor to moderate product yields (39-45%) under similar conditions (Table 3, entries 4 to 9). While the reaction proceeded sluggishly in CH_3CN (Table 3, entries 10). This solvents plays a negative role by retarding the multi-component pathway. This might be due to the adsorption of solvent on the catalyst surface or the solvent-reactant interactions. Although water and ethanol were proved to be capable of promoting the reaction, in this case, IL destruction and silica chromatography needed to be used in order to separate and purify the product (Table 3, entries 1 and 2). Interestingly, the trial reaction in the presence of IL and in the absence of solvent afforded the desired product **4a** under solvent-free condition in high to quantitative yields and less reaction time compared to other refered solvents (Table 3, entry 11).

Table 3. Optimization of the reaction conditions in different solvents. [a]

Entry	Solvent	Amount of catalyst (mol%)	Temperature (°C)	Reaction time (min)	Yield (%) [b]
1	Water	10	80	30	25
2	EtOH	10	80	30	20
3	PEG	10	80	20	85
4	DMF	10	80	30	45
5	DMSO	10	80	20	34
6	CH_2Cl_2	10	80	40	40
7	$CHCl_3$	10	80	55	42
8	Toluene	10	80	52	39
9	CH_3CN	10	80	20	34
10	----	10	80	4	96

[a] Reaction conditions: a mixture of 2-chlorobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (2 mmol) and Li(Glycine)(CF_3SO_3) (1 ml). [b] Isolated yield.

Furthermore, a comparative evaluation of the catalytic efficacy of Li(Glycine)(CF_3SO_3) was compared with some of the obtained results in this study with those methodologies which have been reported using other earlier homogeneous and heterogeneous catalysts for the synthesis of 3,4-dihydropyrimidine-2-(1H)-one. It is obvious that a superior methodology in term the use of a renewable catalyst without any post-modification and catalyst loading in most cases has been developed. A demonstrated in Table 4, our method is simpler, efficient, and less time consuming for the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro pyrimidin-2(1*H*)-one.

Table 4. Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro pyrimidin-2(1*H*)-one using different catalysts.

Entry	Catalyst and Conditions	Reaction time (h)	Yield(%) [b]	References

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1	Silica sulfuric acid/EtOH/heat	6	91	42
2	Sulfated tungstate/Solvent-free/80^{o}C	1	92	43
3	$BF_3.OEt_2$/CuCl/THF/reflux	18	71	28
4	$Cu(OTf)_2$ /EtOH/100 ^{o}C/MW	1	95	45
5	CD-SO_3H/Solvent-free/80 ^{o}C	2	89	46
6	PPA-SiO_2/CH_3CN/reflux	1	88	32
7	DBSA/Water/54 ^{o}C	7	89	47
8	IRMOF-3/Solvent-free/reflux	5	89	48
10	Chiral phosphoric acid/CH_2Cl_2/25 ^{o}C	4 days	77	56
11	bentonite-/PS-SO_3H/Solvent-free /120 ^{o}C	35min	84	57
12	$Ce(C_{12}H_{25}SO_3)$ /EtOH/80 ^{o}C	8	83	58
13	$SnCl_2$-nano SiO_2/EtOH/reflux	40min	92	59
14	Li(Glycine)(CF_3SO_3) /Solvent-free/80^{o}C	4 min	96	This work

In order to study the generalize of this procedure, a series of 3,4-dihydropyrimidine-2-(1H)-one derivatives (**4a-v**) were prepared in excellent yields from different aromatic aldehydes having electron-donating as well as electron-withdrawing groups under the optimal conditions. These results are listed in Table 5. The nature of the functional group on the aromatic ring of the aldehyde exerted a strong influence on the reaction time. It was observed that aromatic aldehydes with both electron-donating and electron-withdrawing groups reacted smoothly to gave the corresponding product in high yield (Table 5, entries **4b-t**). Introduction of the electron-donating substituents, such as Me and OMe, caused a decrease of the cytotoxic activity while no significant effect on the cytotoxic activity was observed for the electron-withdrawing substituents such as CN and NO_2. Halogen substituted aromatic aldehydes were employed under the reaction conditions excellent yields (92-98%) of the corresponding products (**4b-h**) were obtained. The *orto* and *para*-substituted gave good results in short time compared to the *meta*-substituted as there is more steric hindrance for the meta substituted aldehydes such as *m*-(OMe, -F, -Cl, -Br, -NO_2) with the use of Li(Glycine)(CF_3SO_3) catalysts. Insertion of halogens like F, Cl or Br into the aryl group as in (**4b-h**), induces an increase of the cytotoxicity. These results clearly indicate that the reactions can tolerate a wide range of differently substituted aldehydes.

Table 5. The Li(Glycine)(CF_3SO_3) catalyzed three-component Biginelli coupling[a]

Entry	R	Yield[b] (%)	Time (min)	Mp[c] (°C) found	Mp (°C) (Lit)
4a	C_6H_5–	97	40	203-205	202-203[53]
4b	2-(Cl)–C_6H_4–	98	35	216-219	215-218[29]
4c	3-(Cl)–C_6H_4–	95	35	193-195	192-193[48]
4d	4-(Cl)–C_6H_4–	97	35	211-213	212-214[26]
4e	3-(Br)–C_6H_4–	94	30	185-187	185-186[55]
4f	2,4-$(Cl)_2$–C_6H_3–	96	30	249-251	251-252[54]
4g	3,4-$(Cl)_2$–C_6H_3–	93	35	223-225	222-223[49]
4h	4-(F)–C_6H_4–	94	30	178-180	175-177[22]
4i	2-(NO_2)–C_6H_4–	95	35	218-220	220-222[51]
4j	3-(NO_2)–C_6H_4	93	37	225-227	226-228[53]
4k	4-(NO_2)–C_6H_4–	97	35	211-213	208-211[28]
4l	2-(OCH_3)–C_6H_4–	93	37	258-260	259-260[42]
4m	3-(OCH_3)–C_6H_4–	91	37	208-210	207-208[28]
4n	4-(OCH_3)–C_6H_4–	92	37	203-205	203-204[53]

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4o	3,4-$(OCH_3)_2$–C_6H_3–	90	40	176-178	174-176[49]
4p	3-(CH_3O)-4-(HO) –	91	40	231-233	233-235[53]
4q	4-(CF_3)–C_6H_4–	93	30	177-179	173-175[50]
4r	2-(HO)–C_6H_4–	91	40	198-200	199-201[52]
4s	4-(HO)–C_6H_4–	92	40	229-231	231-233[53]
4t	4-(CH_3)–C_6H_4–	90	40	215-216	216-217[50]
4u	C_6H_5-CH=CH	85	40	227-229	234-236[53]
4v	2-Furyl	83	40	204-206	205-207[53]

[a] Reaction conditions: aldehyde (1mmol), ethyl acetoacetate (1 mmol), urea (2 mmol) and Li(Glycine)(CF_3SO_3) (10 mol%), 80 °C; [b] Isolated yield; [c] Melting points are uncorrected.

In the next phase of study, the recovery and reuse cycle of Li(Glycine)(CF_3SO_3) was also evaluated. Hence, we investigated the recyclability of Li(Glycine)(CF_3SO_3) for five consecutive cycles to afforded of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**). As shown in Fig. 4, this ionic liquid can be recycled at least five times without significant decrease in catalytic activity, the yields ranged from 97% to 94%.

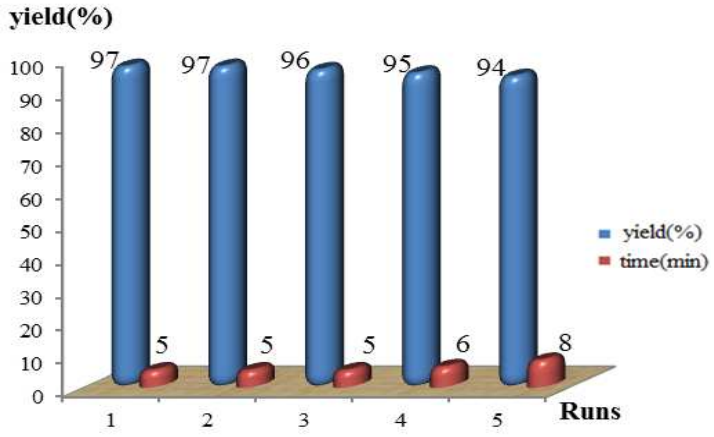

Fig. 4. Reusability of the catalyst.

According to these observations, a possible mechanism for the formation of 3,4-dihydro pyrimidin-2(1*H*)-one is shown in Scheme 2. The reaction occurs via initial formation of the acylimine intermediate (**5**) by nucleophilic addition of urea (**3**) to aldehyde (**1**) followed by dehydration. In this stage, activated 1,3-dicarbonyl compound is attack to the acylimine intermediate and an open-chain ureide (**6**) be formed which underwent intramolecular cyclization to afford the final product (**4**).

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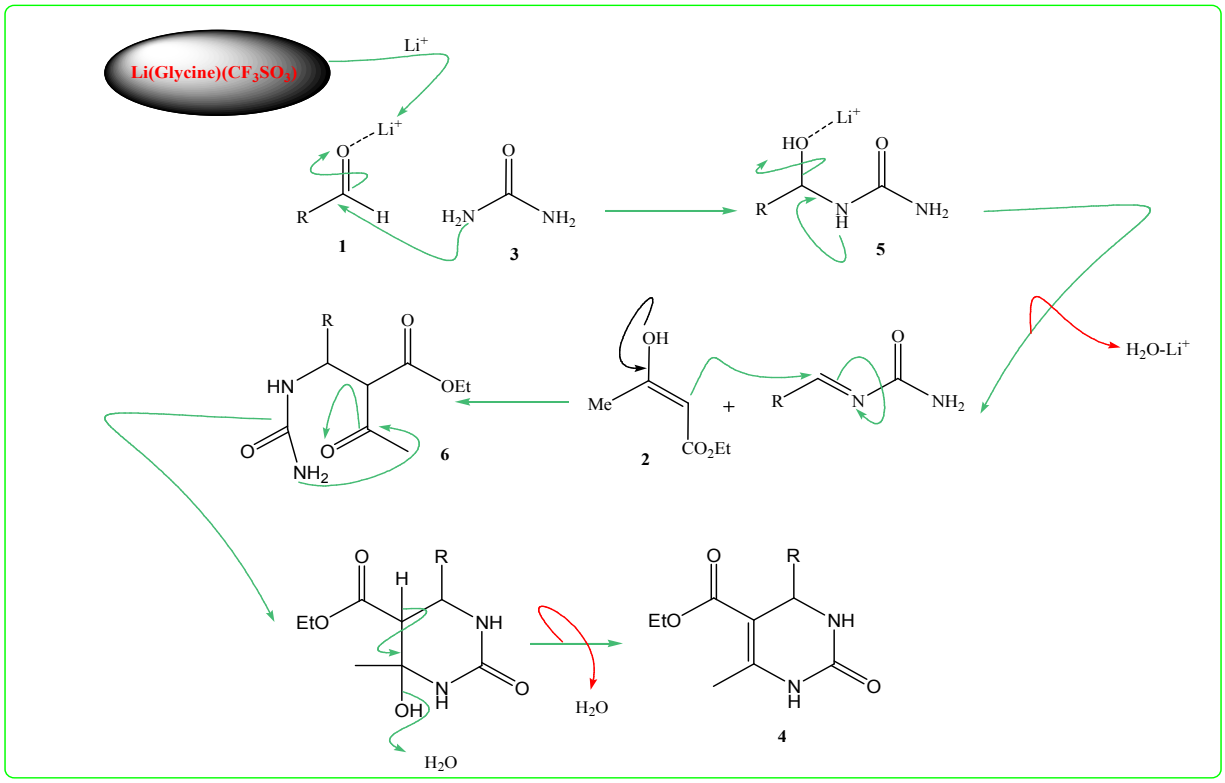

Scheme 2. A plausible mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones(**4**).

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Li(Glycine)(CF_3SO_3) as an effective and recoverable catalyst for the preparation of 3,4-dihydropyrimidine-2-(1H)-one under solvent-free conditions

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