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One-Pot Three-Component Biginelli-Type Reaction To Synthesize 5-Carboxanilide-Dihydropyrimidinones Catalyzed By Ionic Liquids In Aqueous Media

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Abstract: For the first time, 5-carboxanilide-dihydropyrimidinones have been synthesized in good yields by a modified Biginelli-type reaction with dicationic acidic ionic liquids as catalysts. The products could be separated simply from the catalyst-water system, and the catalysts could be reused at least six times without noticeably reducing catalytic activity.
Keywords: Biginelli-type reaction, 5-carboxanilide-dihydropyrimidinones, Dicationic ionic Liquid, cyclocondensation, one-pot synthesis.

INTRODUCTION

Dihydropyrimidinones and their derivatives have attracted increasing interest owing to their therapeutic and pharmaceutical properties, such as antiviral, antibacterial, anti-inflammatory and antitumour activities.[1-3] Recently, functionalized dihydropyrimidinones have been successfully used as antihypertensive agents, calcium channel blockers, adrenergic and neuropeptide Y (NPY) antagonists.[4,5] In addition, some alkaloids containing the dihydropyrimidine core unit which also exhibit interesting biological properties have been isolated from marine sources. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors.[6,7]

The original protocol for the synthesis of dihydropyrimidinones, reported by Biginelli in 1893,
involves a one-pot reaction of benzaldehyde, ethyl acetoacetate and urea in ethanol under strongly acidic conditions.[8] However, this method suffers from drawbacks such as low yields (20-40%) of the desired products, particularly in case of substituted aldehydes, and loss of acid sensitive functional groups during the reaction. This has led to multi-step synthetic strategies that produce somewhat better yields, but which lack the simplicity of the original one-pot Biginelli protocol.[9] The search for more suitable preparation of dihydropyrimidinones continues today.

Recently, many synthetic methods for preparing these compounds have been developed to improve and modify this reaction by using Lewis acid catalysts as well as protic acids including $FeCl_3 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$,[10] lanthanide triflate,[11] H_3BO_3,[12] VCl_3,[13] $Sr(OTf)_2$,[14] PPh_3,[15] Indium(III) halides,[16] LiBr,[17] Silica sulfuric acid,[18] $Mn(OAc)_3 \cdot 2H_2O$[19], $Y(NO_3)_3 \cdot 6H_2O$,[20] $In(OTf)_3$,[21] $TaBr_5$,[22] $Ce(NO_3)_3 \cdot 6H_2O$,[23] silica chloride,[24] HCOOH,[25] $SrCl_2 \cdot 6H_2O$-HCl,[26] $Yb(OTf)_3$,[27] $Bi(NO_3)_3 \cdot 5H_2O$,[28] tungstate sulfuric acid,[29] $HClO_4$-SiO_2[30] and so on. In addition, ionic liquids,[31]

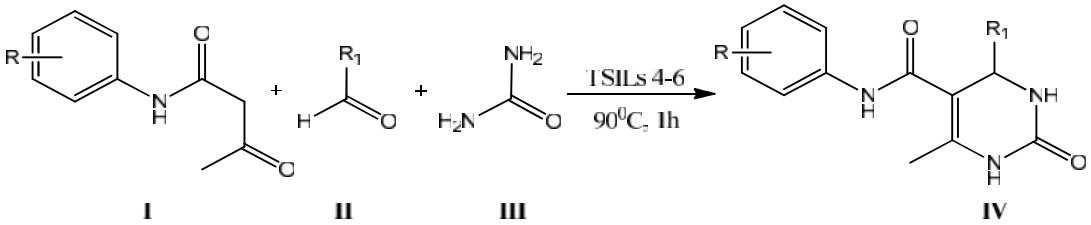
microwave irradiation[32] and ultrasound irradiation[33] were also utilized as the catalytic condition. However, in spite of their potential utility, many of these methods involve expensive reagents, strong acidic conditions and long reaction times.

Nowadays ionic liquids attract much interest as environmentally benign catalysts or excellent alternatives to organic solvents, because of their favorable properties, for example negligible volatility and high thermal stability. Brønsted acidic or basic task-specific ionic liquids (TSILs) are designed to replace traditional acids or bases as catalysts in organic synthetic procedures. In view of the advantages and disadvantages of homogeneous and heterogeneous catalytic reactions, the use of TSILs as reaction medium and/or catalytic system may be a convenient solution to the solvent-emission and catalyst-recycling problems. TSILs have also been used as catalysts for the Biginelli reaction.[34-39]

In continuation of our study of recycled compounds catalyzed MCRs,[40] we synthesized some dicationic acidic ionic liquids as halogen-free TSILs that bear dialkane sulfonic acid groups in acyclic diamine cations (Scheme 2), and subsequently used these as catalysts in a one-pot, three-component Biginelli-type reaction (Scheme 1). To the best of our knowledge of the open literature, Biginelli-type reactions catalyzed by dicationic ionic liquids have not been reported.

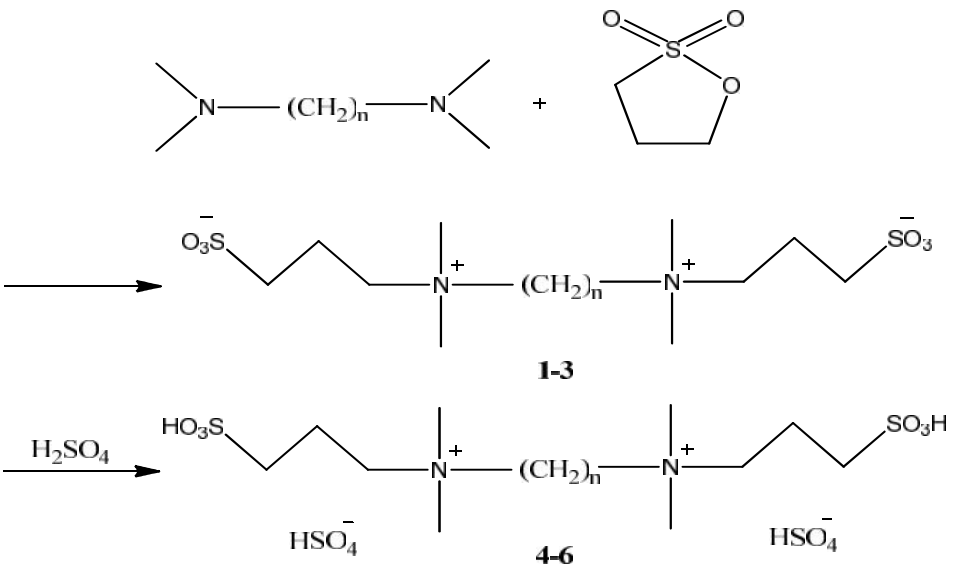
MATERIALS AND METHODS

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). All reagents were purchased from Fluka, Sigma Aldrich, Merck and Rankem and used without further purification.



I **II** **III** **IV**

Scheme-1



1-3

4-6

1,4: n=2, **2,5:** n=3, **3,6:** n=6

Scheme-2

N,N,N^1,N^1-Tetramethylethylenediammoniumbis(propanesulfonate) (1, $C_{12}H_{28}N_2O_6S_2$)

To a solution of 11.6 g tetramethylethylene diamine (0.10 mol) in 20 cm^3 1,2-dichloroethane was added 24.4 g 1,3-propanesulfone (0.20 mol), in portions, within 15 min. The mixture was then stirred under nitrogen for 2 h at 55-60^{0}C. The white precipitate thus formed was cooled to room temperature, then isolated by filtration and washed with petroleum ether. The product was recrystallized from a mixture of water, ethanol, and diethyl ether to give 98% yield of white solid product, m.p.: 298–300^0 C (dec). ^{1}H NMR (300 MHz): δ = 2.12–2.20 (m, 2x 2H, N–C–CH_2–C–SO_3), 2.88 (t, 2x 2H, J = 6.9 Hz, N–C–C–CH_2–SO_3), 3.14 (s, 4x 3H, N–CH_3), 3.49–3.52 (m, 2x 2H, N–CH_2–C–C–SO_3), 3.87 (s, 4H, N–CH_2–CH_2–N) ppm; MS: m/z = 361.06 (M^+).

N,N,N^1,N^1-Tetramethyl-1,3-propandiyl diammoniumbis(propanesulfonate) (2, $C_{13}H_{30}N_2O_6S_2$)

Synthesized by the same process as **1** except that the reaction was carried out for 4 h at 35-40^0 C. White solid, yield 96%, m.p.: 292–294^0 C (dec). ^{1}H NMR (300 MHz): d = 2.06–2.14 (m, 2x 2H, N–C–CH_2–C–SO_3), 2.18–2.20 (m, 2H, N–C–CH_2–C–N), 2.85 (t, 2x 2H, J = 6.8 Hz, N–C–C–CH_2–SO_3), 3.03 (s, 4x 3H, N–CH_3), 3.30 (t, 2x 2H, J = 8.0 Hz, N–CH_2–C–C–SO_3), 3.41 (t, 4H, J = 8.3 Hz, N–CH_2–C–CH_2–N) ppm; MS: m/z = 374.30 (M^+ -1).

N,N,N^1,N^1-Tetramethyl-1,6-hexandiyl diammoniumbis(propanesulfonate) (3, $C_{16}H_{36}N_2O_6S_2$)

Synthesized by the same process as **1** except that the reaction was carried out for 2 h at 55-60^0 C. White solid, yield 95%, m.p.: 300–303^0 C (dec). ^{1}H NMR (300 MHz): d = 1.30 (s, 4H, N–C–C–CH_2–CH_2–C–C–N), 1.66 (s, 4H, N–C–CH_2–C–C–CH_2–C–N), 2.04–2.10 (m, 2x 2H, N–C–CH_2–C–SO_3), 2.84 (t, 2x 2H, J = 7.1 Hz, N–C–C–CH_2–SO_3), 2.96 (s, 4x 3H, N–CH_3), 3.20 (t, 2x 2H, J = 8.4 Hz, N–CH_2–C–C–SO_3), 3.33 (t, 4H, J = 8.5 Hz, N–CH_2–C–C–C–C–CH_2–N) ppm; MS: m/z = 417.13 (M^+).

N,N,N^1,N^1-Tetramethyl-N,N^1-bis(3-sulfopropyl) ethylenediammonium bis(hydrogensulfate) (4, $C_{12}H_{32}N_2O_{14}S_4$)

To a solution of 36.1 g **1** (0.10 mol) in 10 cm^3 water was added 20.0 g sulfuric acid solution (98%, 0.20 mol). The mixture was then stirred for 2 h at 80^{0}C. The water was then removed under vacuum at 100^{0}C and the product was washed repeatedly with diethyl ether to remove unreacted material and again dried under vacuum. TSIL 4 was obtained quantitatively and in high purity as a colorless oil. ^{1}H NMR (300 MHz): d = 1.85–1.95 (q, 2x 2H, J = 7.65 Hz, N–C–CH_2–C–SO_3), 2.64 (t, 2x 2H, J = 6.9 Hz, N–C–C–CH_2–SO_3), 2.89 (s, 4x 3H, N–CH_3), 3.24 (t, 2x 2H, J = 8.4 Hz, N–CH_2–C–C–SO_3), 3.60 (s, 4H, N–CH_2–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): d = 18.71, 47.48, 51.72, 56.30, 64.18 ppm; MS: m/z = 556.89 (M^+), 361.07 (M^+-$2H_2SO_4$, 100).

N,N,N^1,N^1-Tetramethyl-N,N^1-bis(3-sulfo propyl)-1,3-propandiyldiammonium bis(hydrogensulfate) (5, $C_{13}H_{34}N_2O_{14}S_4$)

Synthesized by the same process as **4**, quantitative yield of pale yellow oily product. ^{1}H NMR (300 MHz): d = 2.01–2.11 (m, 4H+2H, N–C–CH_2–C–SO_3, N–C–CH_2–C–N), 2.72–2.81 (m, 2x 2H, N–C–C–CH_2–SO_3), 2.92 (s, 4x 3H, N–CH_3), 3.21–3.32 (m, 4H+4H, N–CH_2–C–C–SO_3, N–CH_2–C–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): d = 17.14, 19.09, 48.10, 52.33, 61.15, 63.77 ppm.

N,N,N^1,N^1-Tetramethyl-N,N^1-bis(3-sulfopropyl)-1,6-hexandiyldiammonium bis(hydrogensulfate) (6, $C_{16}H_{40}N_2O_{14}S_4$)

Synthesized by the same process as **4**, quantitative yield of pale yellow oily product. ^{1}H NMR (300 MHz): d = 1.13 (s, 4H, N–C–C–CH_2–CH_2–C–C–N), 1.49 (s, 4H, N–C–CH_2–C–C–CH_2–C–N), 1.88–1.90 (m, 2x 2H, N–C–CH_2–C–SO_3), 2.64–2.68 (m, 2x 2H, N–C–C–CH_2–SO_3), 2.79 (s, 4x 3H, N–CH_3), 3.00–3.02 (m, 2x 2H, N–CH_2–C–C–SO_3), 3.13–3.15 (m, 4H, N–CH_2–C–C–C–C–CH_2–N) ppm; ^{13}C NMR (75.5 MHz): d = 17.92, 21.42, 24.74, 47.15, 50.40, 61.85, 63.84 ppm.

General procedure for the synthesis of 5-Carboxanilide-tetrahydropyrimidines

A mixture of an appropriate aldehyde **II** (10 mmol, 1.0 equiv), *N*-phenyl-3-oxobutanamide **I** (10 mmol, 1.0 equiv), urea **III** (15 mmol, 1.5 equiv) in 10 cm^3 H_2O was added 0.2 mmol **4**. The mixture was stirred at 90^0 C until TLC indicated the starting materials had disappeared. The reaction mixture was cooled to room temperature and poured onto ice (100 g). The resulting precipitate was collected by simple filtration and the solid was washed with a small amount of methanol and diethyl ether. The solid was recrystallized from ethanol to yield N-phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxamide derivatives as a white to pale yellow solid in 70-95 % yield.

***N*-(3-(Trifluoromethyl)phenyl)-4-phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (IVa).** Mp 208–210^{0}C; Yield - 79%. IR (KBr): 3289, 3276, 3234, 3010, 2956, 1689, 1672, 1554, 1345, 1220, 1108, 789 cm^{-1}; ^{1}H NMR: δ = 10.17 (s, 1H, NH), 9.95 (s, 1H, NH), 8.39 (s, 1H, NH), 8.09–7.27 (m, 9H, Ar), 5.46 (s, 1H, CH), 1.61 (s, 3H, CH_3); Mass: *m/z* = 375 [M^+]; ^{13}C NMR (400 MHz, DMSO) δ 14.13 (CH_3), 51.12 (C4), 108.73 (C5), 120.54, 121.16, 125.81, 126.19, 127.34, 128.50, 128.68, 130.08, 130.31, 130.36, 132.17 and 133.00 (C Ar.), 125.71 (CF_3), 134.08 (C-C4, Ar), 137.34 (C-NH, Ar), 146.35 (C6), 151.05 (C2, CO), 164.35 ($CONH_2$); Anal. Calcd for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30; N, 11.20. Found: C, 60.77; H, 4.28; N, 11.21.

***N*-(3-(Trifluoromethyl)phenyl)-4-(3-chloro phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (IVb).** Mp 216–218^{0}C; Yield - 69%. IR (KBr): 3408, 3298, 3271, 3088, 2928, 1672, 1654, 1506, 1442, 1334, 1122, 792 cm^{-1}; ^{1}H NMR: δ = 10.14 (s, 1H, NH), 9.98 (s, 1H, NH), 8.45 (s, 1H, NH), 8.09–7.22 (m, 8H, Ar), 5.46 (s, 1H, CH), 1.64 (s, 3H, CH_3); Mass: *m/z* = 409 [M^+]; Anal. Calcd for $C_{19}H_{15}ClF_3N_3O_2$: C, 55.69; H, 3.69; N, 10.25. Found: C, 55.62; H, 3.67; N, 10.22.

***N*-(3-(Trifluoromethyl)phenyl)-4-(furan-2-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine -5-carboxamide (IVc).** Mp 222–224^{0}C; Yield - 90%. IR (KBr): 3290, 3282, 3271, 3088, 2856, 1690, 1672, 1376, 1222, 1022, 756 cm^{-1}; ^{1}H NMR: δ = 10.04 (s, 1H, NH), 9.97 (s, 1H, NH), 8.40 (s, 1H, NH), 7.84–6.79 (m, 7H, Ar), 4.96 (s, 1H, CH), 1.73 (s, 3H, CH_3); Mass: *m/z* = 365 [M^+]; Anal. Calcd for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.85; H, 3.84; N, 11.49.

***N*-(3,4-Dichlorophenyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (IVd).** Mp 192–194^{0}C; Yield - 73%. IR (KBr): 3450, 3209, 3072, 2847, 1691, 1676, 1600, 1510, 1425, 1342, 1172, 1023, 769 cm^{-1}; ^{1}H NMR: δ = 9.70 (s, 1H, NH), 8.92 (s, 1H, NH), 8.42 (s, 1H, NH), 7.94–7.15 (m, 7H, Ar), 5.00 (s, 1H, CH), 1.73 (s, 1H, CH_3); Mass: *m/z* = 410 [M^+]; Anal. Calcd for $C_{18}H_{14}Cl_3N_3O_2$: C, 52.64; H, 3.44; N, 10.23. Found: C, 52.61; H, 3.45; N, 10.21.

***N*-(3,4-Dichlorophenyl)-4-(4-nitrophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (IVe).** Mp 186–188^{0}C; Yield - 92%. IR (KBr): 3284, 3228, 3117, 2933, 2854, 1693, 1666, 1622, 1442, 1338, 1238, 1128, 773 cm^{-1}; ^{1}H NMR: δ = 10.25 (s, 1H, NH), 9.85 (s, 1H, NH), 8.20-7.24 (m, 7H, Ar), 5.07 (s, 1H, CH), 1.62 (s, 3H, CH_3); Mass: *m/z* = 421 [M^+]; Anal. Calcd for $C_{18}H_{14}Cl_2N_4O_4$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.27; H, 3.31; N, 13.34.

***N*-(3,4-Dichlorophenyl)-4-propyl-1,2,3,4-tetra hydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (IVf).** Mp 184–186^{0}C; Yield - 97%. IR (KBr): 3286, 3272, 2976, 2842, 1684, 1456, 1361, 1222, 1072, 740 cm^{-1}; ^{1}H NMR: δ = 10.44 (s, 1H, NH), 9.57 (s, 1H, NH), 7.60-7.19 (m, 3H, Ar), 6.87 (s, 1H, NH), 4.95 (s, 1H, CH), 3.65–3.31 (m, 2H, CH_2), 2.61–2.14 (m, 2H, CH_2), 1.58–1.39 (m, 3H, CH_3), 0.94 (s, 3H, CH_3); Mass: *m/z* = 342 [M^+]; Anal. Calcd for $C_{15}H_{17}Cl_2N_3O_2$: C, 52.64; H, 5.01; N, 12.28. Found: C, 52.61; H, 4.96; N, 12.28.

***N*-(4-Nitrophenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (IVg).** Mp 262–264^{0}C; Yield - 72%. IR (KBr): 3279, 3244, 3225, 3190, 2852, 1693, 1674, 1614, 1529, 1448, 1357, 1240, 758 cm^{-1}; ^{1}H NMR: δ = 9.97 (s, 1H, NH), 8.19 (s, 1H, NH), 8.16 (s, 1H, NH), 7.89–6.96 (m, 8H, Ar), 4.96 (s, 1H, CH), 1.68 (s, 3H, CH_3); Mass: *m/z* = 370 [M^+]; Anal. Calcd for $C_{18}H_{15}FN_4O_4$: C, 58.38; H, 4.08; N, 15.13. Found: C, 58.37; H, 4.04; N, 15.10.

***N*-(4-Nitrophenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro--6-methyl-2-oxopyrimidine-5-carboxamide (IVh).** Mp 210–212^{0}C; Yield - 85%. IR (KBr): 3373, 3248, 3211, 3090, 1689, 1678, 1600, 1529, 1354, 1207, 1186, 840, 758 cm^{-1}; ^{1}H NMR: δ = 10.21 (s, 1H, NH), 8.91 (s, 1H, NH), 8.54 (s, 1H, NH), 8.18–6.84 (m, 8H, Ar), 4.89 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 1.74 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO) δ 14.73 (CH_3), 52.39 (C4), 58.93 (OCH_3), 108.66 (C5), 114.39, 114.63, 121.17, 121.54, 127.55, 128.57, 129.35 and 130.06 (C Ar.), 131.88 (C-C4, Ar.), 134.25 (C-NH, Ar), 136.98 (C-NO_2), 145.00 (C6, C-CH_3), 157.05 (C2, C=O), 159.43 (C-OCH_3), 163.75 (CONH); Mass: *m/z* = 382 [M^+]; Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.66; H, 4.71; N, 14.63.

***N*-(4-Nitrophenyl)-4-propyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (IVi).** Mp 222–224^{0}C; Yield - 95%. IR (KBr): 3308, 3296, 3277, 2954, 2848, 2822, 1688, 1668, 1545, 1442, 1345, 1207, 1112, 786 cm^{-1}; ^{1}H NMR: δ = 9.03 (s, 1H, NH), 8.51 (s, 1H, NH), 8.25 (s,

1H, NH), 7.38–6.78 (m, 4H, Ar), 5.75 (s, 1H, CH), 3.16-3.13 (m, 2H, CH_2), 2.52–2.49 (m, 2H, CH_2), 1.98 (s, 3H, CH_3), 1.77–1.72 (m, 3H, CH_3); Mass: *m/z* = 318 [M^+]; Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.57; H, 5.66; N, 17.57.

RESULTS AND DISCUSSION

The procedure for synthesis of catalyst TSILs was made up of a two-step atom-economic reaction. The zwitterionictype precursors were prepared by a one-step direct sulfonation reaction. Acidification of the zwitterions was accomplished by mixing with twice the molar amount of sulfuric acid (98%, aq.) to convert the pendant sulfonate group into dicationic halogen-free acidic ionic liquids. The chemical yields for both zwitterion formation and acidification were essentially quantitative, because neither reaction produced byproducts. The fresh new catalysts are somewhat viscous pale yellow liquids at room temperature. All the catalysts produced are entirely miscible with water and soluble or partly soluble in organic solvents.

In the initial catalytic activity experiments, 4-nitrobenzaldehyde, 3,4-dichloro acetoacetanilide, and urea were employed as the model reactants at 90^0 C in TSILs for catalytic performance of the TSILs (Table 1). It was shown that no desirable product could be detected when a mixture of 4-nitrobenzaldehyde, 3,4-dicchloro acetoacetanilide, and urea was heated at 90^0 C for 1h in the absence of TSILs (entry 1), which indicated that the catalysts was absolutely necessary for this three-component Biginelli-type reaction. All TSILs proved to be very active. It is clear that the yield was increased by addition of TSILs and the optimum amount of TSILs was 2 mol% (entries 3, 7). A larger amount of the catalysts could not improve the yield.

This condensation reaction with various aldehydes, acetoacetanilides, and urea in the presence of TSIL 1 as the catalyst was then explored under the optimized reaction conditions described above; the results are presented in Table 3. It can easily be seen that this three-component Biginelli-type condensation was complete within 1h. Compared with the classical Biginelli method, one additional important feature of the present procedure is the ability to tolerate variations in both aldehydes and acetoacetanilides simultaneously.

A variety of substituted aromatic, aliphatic and hetero-aromatic aldehydes, with either electron-donating or electron-withdrawing groups, provided favorable results in this reaction. For example, 5-carboxanilide-dihydropyrimidinones generated from 4-nitro benzaldehyde and 2-furyl aldehyde afforded the corresponding products in greater than 90% yield. Aliphatic aldehydes were equally amenable to these conditions with *n*-butyraldehyde providing the 5-carboxanilide-dihydro pyrimidinone in 95 to 97% yield. Halogenated aromatic substitution at the 4-position of the DHPM could also be achieved using this methodology, albeit in significantly lower yields (Table 2 entries 2, 4 and 7).

Table 1: Effect of the different catalysts on the Biginelli-type reaction

Entry	Catalyst (mmol)	Isolated Yield (%)
1	0	0
2	**4** (0.1)	84
3	**4** (0.2)	92
4	**4** (0.3)	92
5	**4** (0.4)	90
6	**5** (0.1)	86
7	**5** (0.2)	92
8	**5** (0.3)	92
9	**6** (0.1)	84
10	**6** (0.2)	90
11	**6** (0.3)	90

Reaction conditions: 4-nitro benzaldehyde (10mmol), 3,4-dichloro acetoacetanilide (10 mmol), urea (15 mmol) 0.2 mmol TSILs, 90^0C, 1h.

The recycling performance of the catalysts was also investigated using the above model reaction. After separation of the products, the filtrate containing the catalyst was reused in the next run without further purification. A mixture of 4-nitrobenzaldehyde, 3,4-dichloroacetoacetanilide, and urea in stoichiometric ratio was added to the filtrate and stirred under the same conditions. The data listed in **Table 3** show that the TSILs could be reused six times without a decrease of catalytic activity. Compared with the traditional solvents and catalysts, the easy recycling performance is also an attractive property of the TSILs for environmental protection and economic reasons.

CONCLUSION

In summary a new method for the preparation of 5-carboxanilide-DHPMs was discovered that utilizes a multicomponent coupling reaction catalyzed by dicationic ionic liquids, with a rapid and high yielding cyclocondensation to afford the corresponding DHPMs. The use of dicationic ionic liquids was well tolerated with a range of aldehydes and ketones. The methodology has the advantages of high yields, lack of organic solvent, recyclability of catalysts, and easy workup for isolation of the products with high purity.

Table-2: A general one-pot Biginelli reaction to generate 5-carboxanilide-4-substituted dihydropyrimidinones

Entry	R	R_1	Product	Yield[a] (%)	M.P (^oC)
1	3-CF_3	Phenyl	**IVa**	79	208-210
2	3-CF_3	3-chloro Phenyl	**IVb**	69	216-218
3	3-CF_3	2-furyl	**IVc**	90	222-224
4	3,4-dichloro	3-chloro Phenyl	**IVd**	73	192-194
5	3,4-dichloro	4-nitro Phenyl	**IVe**	92	186-188
6	3,4-dichloro	n-Propyl	**IVf**	97	184-186
7	4-NO_2	4-F Phenyl	**IVg**	72	262-264
8	4-NO_2	4-OCH_3 Phenyl	**IVh**	85	210-212
9	4-NO_2	n-Propyl	**IVi**	95	222-224

[a] Isolated yields after purification.

Table 3: Reuse of the dicationic ionic liquid catalysts

Run	Isolated Yield (%)		
	4	**5**	**6**
1	92	92	92
2	92	92	92
3	90	89	90
4	89	87	88
5	88	86	85
6	87	84	83

Reaction conditions: 4-nitro benzaldehyde (10mmol), 3,4-dichloro acetoacetanilide (10 mmol), urea (15 mmol) 0.2 mmol TSILs, 90^0C, 1h. After separation of the product by filtration, the recovered solvent containing the catalyst was reused directly.

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