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Novel acidic ChCl/TFA DES as reaction medium and catalyst for Biginelli and Hantzsch reactions

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ABSTRACT

Novel deep eutectic solvent (DES) using Choline Chloride (ChCl) as the hydrogen bond acceptor and triflouroacetic acid (TFA) as hydrogen bond donor (1.0:1.5 molar ratio) was prepared at room temperature and characterized by FT- IR and ^{1}H NMR spectroscopy. Also, this novel acidic RTDES (room temperature deep eutectic solvent) was successfully used both as a reaction medium and catalyst in Biginelli, Biginelli-like, and Hantzsch reactions. The procedures have the advantages of high yields, short reaction times and easy work-up as well as relatively mild conditions and they do not require additional catalysts and organic solvents. The DES could be easily recycled without considerable loss of activity even after more than three cycles.

***Keywords**: Deep eutectic mixture, Choline chloride, Triflouroacetic acid, Biginelli reaction, Hantzsch reaction.*

1. Introduction

A new generation of solvents, named Deep Eutectic Solvents (DESs), was presented by Abbott and co-workers in 2003 for the first time as suitable alternative solvents compared to conventional and unconventional solvents, such as ionic liquids (ILs) [1]. DESs are currently attracting widespread scientific and technological interest as low cost alternatives and excellent physico-chemical properties. A DES is a fluid generally composed of two or more components that are capable of self-association, often through hydrogen bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component. [2,3].

Multicomponent reactions (MCRs) constitute one of the most efficient tools in modern synthetic organic chemistry, since they have all features that contribute to an ideal synthesis: high atom efficiency, quick and simple implementation, time and energy saving, environment-friendly aspect and they offer a target and diversity-oriented synthesis [4]. Thus MCRs are a valuable strategy in the "green chemistry toolbox".

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The combination of MCR with DES is, therefore, one of the most suitable strategies for developing libraries of useful scaffolds. The Biginelli [5] and Hantzsch [6] reactions are the most notable and well-known MCRs for the preparation of 3,4-dihydropyrimidone (DHPM) and 1,4-Dihydropyridine (1,4-DHP) scaffolds [7-9]. The 1,4-dihydropyridine nucleus serves as the scaffold for important cardiovascular drugs, which exert their antihypertensive and antianginal actions through actions at voltage-gated calcium channels of the CaV1 (L-type) class [10]. Literature survey shows that several modifications have been developed over the past decade for Hantzsch reaction using different catalysts, such as montmorillonite K10 clay [11], ascorbic acid [12], α-Al_2O_3 [13], carbon microsphere-supported copper nanoparticles [Cu-NP/C] [14], ionic liquid based organosilica supported Fe/m*eso*-tetrakis(4-sulfonatophenyl)porphyrin complex [ILOS@Fe/TSPP] [15], ionic liquid based silica coated nano-Fe_3O_4 [16], Cd-MOF [17], silica supported 12-tungstophosphoric acid [18], and alginic acid [19].

Dihydropyrimidinones (DHPMs), the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers, antihypertensive agents, and alpha-1a antagonists [20]. Different synthetic procedures have been reported for preparing

DHPMs via Biginelli reaction [21-27]. Though conventional Biginelli reaction involves acid-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) using aldehydes, (thio) urea, and β- ketoesters (as active methylene compounds) [28], in the Biginelli-like reaction ketones have been used as the source of active methylene [29-39].

Trifluoroacetic acid (TFA) is one of the strongest organic acids; it is widely used in the synthesis reactions as a solvent [40], catalyst [41] and reagent [42]. Herein, we report the preparation of novel CF_3COOH-based DES, and then using it both as a solvent and an acidic catalyst in Hantzsch, Biginelli and Biginelli-like reactions.

2. Experimental

2.1. Materials and instrument

All chemicals were purchased from Fluka and Merck chemical companies. All the reactions were monitored by thin layer chromatography (TLC). FT-IR spectra were recorded on a Bruker PS-15 spectrometer. The ^1H and ^{13}C NMR spectra were taken on Bruker SP-400 Avance spectrometers. A DSC (differential scanning calorimeter Linseis Instrument Model DSC-PT10) was purged of nitrogen. Viscosity was measured in an Ubbelohde-type viscometer, which has a flow time of about 200 s for water at 298.15 K. The viscometer was calibrated with doubly distilled deionized water. Density and speed of sound data were determined by a commercial density and speed of sound measurement instrument (Anton Paar DSA 5000 densitometer and speed of sound analyzer), with an estimated precision of $\pm 5\times10^{-6}$ gcm^{-3} and ±0.5 ms^{-1}, respectively. All physical properties were measured at 298.15 K temperature. Melting points were measured on an Electro thermal 9100 instrument in open capillaries without correction. All products are characterized by comparison of their spectral data and physical properties with those of authentic samples.

2.2. Preparation of the ChCl/TFA DES mixture

A mixture of Choline chloride (13.96 g, 100 mmol) and triflouroacetic acid (6 mL, 150 mmol) was magnetically stirred at room temperature (45 min) until a clear liquid was formed. The achieved liquid was stored in sealed laboratory vials and kept in a desiccator. The obtained DES was used without any further purification. IR (KBr); $\bar{\nu}$ (cm^{-1}): 3369 (br), 1789 (s), 1487 (m), 1214 (s), 1174 (s), 1053 (m), 955 (m). ^1H NMR (400 MHz, D_2O): δ 2.82 (s, 9H, $(CH_3)_3N$), 3.13 (m, 2H, -CH_2-N), 3.67 (m, 2H, -CH_2-O) ppm.

2.3. Typical procedure for the preparation of 3,4-dihydropyrimidine-2(1H)-ones/thiones 4a–j

A mixture of benzaldehyde (1 mmol, 0.09 mL), ethyl acetoacate (1 mmol, 0.13 mL) and urea (1.25 mmol, 0.08 g) in ChCl/TFA DES (1 mL) was stirred at 70 °C in oil bath for 12 min (Table 2, entry 1). The progress of reaction was monitored by thin-layer chromatography (EtOAc: *n*-Hexane, 1:4). After completion of the reaction, the mixture was cooled to room temperature and water (5 mL) was added and the precipitated solid was filtered, washed with water, and recrystallized from ethanol. Compound **4a** was obtained as a white powder (96% yield, 0.250 g).

*2.3.1. Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**4a**)*

White solid (96%, 0.250 g), Mp 196-198 °C (Lit.[38] 200-201); IR (KBr): $\bar{\nu}$ = 3244, 3109, 2933, 1710, 1650, 1222, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, *J*=7.1 Hz, 3H, CH_3 ester), 2.34 (s, 3H, CH_3-6), 4.06 (q, *J*=7.1 Hz, 2H, CH_2 ester), 5.39 (s, 1H, C(4)-H), 5.76 (s, 1H, NH), 7.21-7.62 (m, 5H, Ar-H), 8.38 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 14.1, 18.6, 55.7, 59.9, 101.3, 126.6, 127.9, 128.7, 143.7, 146.3, 153.3, 167.2 ppm.

*2.3.2. Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate (**4b**)*

White solid (95%, 0.291 g), Mp 210-212 °C (Lit.[39] 210); IR (KBr): $\bar{\nu}$ = 3232, 3117, 2916, 1705, 1647, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J*=7.1 Hz, 3H, CH_3 ester), 2.32 (s, 3H, CH_3-), 4.04 (q, *J*=7.1 Hz, 2H, CH_3CH_2-), 5.32 (s, 1H, C(4)-H), 7.56 (d, *J*=9.3 Hz, 2H, Ar-H), 7.95 (s. 1H, NH), 8.27 (d, *J*=9.3 Hz, 2H, Ar-H), 9.41 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 14.4, 18.2, 54.0, 59.7, 98.5, 124.2, 128.0, 147.1, 149.8, 152.1, 152.3, 165.4 ppm.

*2.3.3. Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(3-methoxyphenyl)-2-oxopyrimidine-5-carboxylate (**4c**)*

White solid (92%, 0.238 g), Mp 200-202 °C (Lit.[38] 205-207); IR (KBr): $\bar{\nu}$ = 3315, 3171, 1663 **,** 1651, 1610, 1466, 1284, 1196, 1027, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 1.10 (t, *J*=7.2 Hz, 3H, CH_3 ester), 2.24 (s, 3H, CH_3-6), 3.73 (s, 3H, -OCH3), 3.90 (m, 2H, CH_2 ester), 5.46 (s, 1H, C(4)-H), 6.81-7.23 (m, 5H, Ar-H, NH), 9.08 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 13.94, 17.63, 48.80, 55.29, 58.93, 106.39, 111.04, 112.32, 120.07, 128.63, 146.17, 148.30, 151.24, 160.45, 167.41 ppm.

*2.3.4. Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-methylphenyl)-2-oxopyrimidine-5-carboxylate (**4d**)*
Yellow solid (94%, 0.257 g), Mp 210-213 °C (Lit.[43] 215-217); IR (KBr): $\bar{\nu}$ = 3242, 3122, 2981, 1724, 1705, 1651, 1495, 1460, 1402, 1288, 1228, 1090, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, *J*=7.2 Hz, 3H, CH_3 ester), 2.26 (s, 3H, CH_3-6), 3.98 (q, *J*=7.2 Hz, 2H, CH_2 ester), 5.10 (s, 1H, C(4)-H), 6.86 (m, 2H, Ar-H), 7.13 (m, 2H, Ar-H), 9.58 (s, 1H, NH), 10.27 (s, 1H,NH) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 19.21, 22.32, 58.63, 64.73, 106.13, 119.04, 132.80, 140.89, 144.93, 158.92, 165.34, 170.19 ppm.

*2.3.5. Ethyl 4-(furan-2-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (**4e**)* Black solid (85%, 0.212 g), Mp 200-203 °C (Lit.[39] 205-206); IR (KBr): $\bar{\nu}$ = 3301, 3250, 2896, 2850, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J*=5.27 Hz, 3H, CH_3 ester), 2.31 (s, 3H, CH_3-6), 4.05 (q, *J*=7.04 Hz, 2H, CH_2 ester), 5.15 (s, 1H, C(4)-H), 6.78-7.15 (m, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.69 (s, 1H, NH), 9.29 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 14.08, 17.61, 49.68, 59.30, 99.71, 123.45, 124.56, 126.60, 148.59, 148.71, 152.19, 164.96 ppm.

*2.3.6. Ethyl 1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (**4f**)* Cream solid (94%, 0.259 g), Mp 202-204 °C (Lit.[25] 204-207); IR (KBr): $\bar{\nu}$ = 3322, 3266, 3176, 3111, 1670, 1575, 1470, 1277, 1197, 1105, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J*=6.9 Hz, 3H, CH_3 ester), 2.36 (s, 3H, CH_3-6), 4.10 (q, *J*=6.9 Hz, 2H, CH_2 ester), 5.39 (s, 1H, C(4)-H), 7.19-7.36 (m, 5H, Ar-H), 7.54 (s, 1H, NH), 8.37 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 13.96, 17.07, 55.01, 59.41, 100.89, 113.79, 127.55, 135.64, 144.68, 158.69, 165.09, 173.95 ppm.

*2.3.7. Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxopyrimidine-5-carboxylate (**4g**)*
Cream solid (90%, 0.289 g), Mp 205-207 °C (Lit.[38] 206-209); IR (KBr): $\bar{\nu}$ = 3328, 3101, 2931, 1708, 1627, 1527 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 1.07 (t, *J*=7.0 Hz, 3H, CH_3 ester), 2.48 (s, 3H, CH_3-6), 3.96 (q, *J*=7.0 Hz, 2H, CH_2 ester), 5.28 (s, 1H, C(4)-H), 7.66 (m, 2H, Ar-H), 7.87 (s, 1H, NH), 8.11 (m, 2H, Ar-H), 9.33 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d6) δ 13.91, 17.78, 53.46, 59.34, 98.26, 120.94, 122.29, 130.16, 132.93, 146.89, 147.64, 149.36, 151.74, 164.99 ppm.

2.4. Typical procedure for the preparation of pyrimidinone derivatives 6a–d

A mixture of 4-bromobenzaldehyde (2 mmol, 0.370 g), urea (1.25mmol, 0.080 g) and cyclohexanone (1 mmol, 0.10 mL) in ChCl/TFA DES (1 mL) was magnetically stirred at 70 °C for 35 min (Table 3, entry 3, **6c**). The reaction progress was monitored by TLC (EtOAc: n-Hexane, 3:2). After completion of the reaction, the mixture was cooled to room temperature and water (5 mL) was added and the precipitated solid was filtered, washed with water, and recrystallized from ethanol. Compound **6c** was obtained as a cream solid (88% yield, 0.417 g).

*2.4.1. 7-(4-bromobenzylidene)-4-(4-bromophenyl)-1,3,4,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (**6a**)*
Yellow solid (94%, 0.432 g), Mp 224-226 °C (Lit.[37] 225), IR (KBr): $\bar{\nu}$ = 3423, 3315, 3030, 2982, 1693, 1490, 1240, 1160, 750cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 2.20-2.60(m, 4H, 2×CH_2), 5.90 (s, 1H, C(4)-H), 6.90(s, 1H, NH), 7.07-7.59(m, 8H, ArH), 9.03 (s, 1H, =CH), 10.12(s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d6) δ 27.9, 28.3, 57.1, 69.8, 116.7, 121.3, 128.6, 128.8, 129.6, 130.5, 132.4, 134.0, 136.5, 138.7, 141.1, 174.4 ppm.

*2.4.2. 4.7-(3-nitrobenzylidene)-4-(3-nitrophenyl)-1,3,4,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (**6b**)*
Pale brown solid (92%, 0.361 g), Mp 230-232 °C (Lit.[37] 234-236), IR (KBr): $\bar{\nu}$ = 3445, 3350, 3050, 2978, 1684, 1484, 1224, 1158 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 1.60-2.40 (m, 4H, 2× CH_2), 4.60 (s, 1H, C(4)-H), 6.60(s, 1H, NH), 7.10-7.34 (m, 8H, Ar-H), 8.0 (s, 1H, HC=), 8.90(s,1H,NH) ppm; ^{13}CNMR (100 MHz, DMSO-d6) δ 26.5, 28.0, 55.1, 113.6, 127.3, 128.4, 128.9, 129.8, 130.2, 130.6,131.4, 132.6, 133.2, 135.4, 137.7, 143.1 ppm.

*2.4.3. 8-(4-bromobenzylidene)-4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one (**6c**)*
Yellow solid (88%, 0.417 g), Mp 273-275 °C (Lit.[38] 273-275), IR (KBr): $\bar{\nu}$ = 3445, 3348, 2929, 2867, 1657, 1456, 1377, 1224, 1157 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 1.50-2.80 (m, 6H, 3 CH_2), 5.55(s, 1H, C(4)-H), 6.70(s, 1H, =CH), 7.22 (s, 1H, NH), 7.30-7.63 (m, 8H, Ar-H), 9.27(s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d6) δ 25.2, 26.9, 28.0, 54.6,113.7, 127.0, 128.0, 128.3, 129.1, 129.5, 130.1, 131.0, 132.6, 133.6, 134.4, 136.8, 142.8, 154.7 ppm.

*2.4.4. 8-(3-nitrobenzylidene)-4-(3-nitrophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one (**6d**)*

Yellow powder (90%, 0.365 g), Mp 202-205 °C (Lit.[44] 205-207), IR (KBr): $\bar{\nu}$ = 3435, 3315, 3046, 2990, 2885, 1690, 1556, 1336, 1242, 1165 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 2.05-2.80 (m, 6H, 3 CH_2), 4.60 (s, 1H, C(4)-H), 6.66 (s, 1H, =CH), 7.24 (s, 1H, NH), 7.18-7.34 (m, 8H, Ar-H), 8.45 (s, 1H, NH) ppm; ^{13}CNMR (100 MHz, DMSO-d6) δ 24.7, 26.5, 28.0, 55.1, 113.6, 127.3, 128.4, 128.9, 129.8, 130.2, 130.6,131.4, 132.6, 133.2, 135.4, 137.7, 143.1, 156.0 ppm.

2.5. General procedure for the synthesis of 1,4-dihydropyridines (8, 9, 10)

*2.5.1. Preparation of ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxoquinoline-3-carboxylate (**9b**)*

A mixture of ethyl acetoacetate (1 mmol, 0.13 mL), dimedone (1 mmol, 0.140 g), 4-nitrobenzaldehyde (1 mmol, 0.151 g) and ammonium acetate (1.25 mmol, 0.096 g) in ChCl/TFA DES (1 mL) was stirred at 70 °C for 5 min (Table 4, entry 5, **9b**). After completion of the reaction, as indicated by TLC (EtOAc: n-Hexane, 3:7), water (5.0 mL) was added and the organic layer was extracted with ethyl acetate (4×10 mL), dried over anhydrous $MgSO_4$ and evaporated. The obtained solid was recrystallized from ethanol (80% yield, 0.308 g).

1,4-dihydropyridines **8** and **10** were synthesized according to the 2.5.1 procedure using 2 mmol ethyl acetoacetate and 2 mmol dimedone, respectively.

2.5.2. *Spectroscopic data for compounds **8, 9, 10***

*2.5.1.1. Diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl pyridine-3,5-dicarboxylate (**8a**)*

Yellow solid (90%, 0.297 g), Mp 158-160 °C (Lit.[45] 160), IR (KBr): $\bar{\nu}$ = 3342, 3060, 2282, 1689, 1651, 1491, 1372, 1218, 1127, 1091,704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J*=7.12 Hz, 6H, 2× CH_3 ester), 2.32 (s, 6 H, CH_3-2,6), 4.04–4.12 (m, 4H, 2× CH_2 ester), 4.99 (s, 1H, C(4)-H), 5.72 (broad s, 1H, NH), 7.09–7.29 (m, 5H, Ar-H) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 14.23, 19.52, 39.66, 59.69, 104.21, 126.07, 127.81, 127.98, 143.79, 147.75, 167.62 ppm.

*2.5.1.2. Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (**8b**)* Yellow solid (95%, 0.356 g), Mp 132-134 °C (Lit.[45] 130-132), IR (KBr): $\bar{\nu}$ = 3350, 3080, 2920, 1707, 1640, 1520, 1485, 1345, 1300, 1210, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, *J*=7.2 Hz, 6H, 2× CH_3 ester), 2.21 (s, 6H, CH_3-2,6), 3.94 (q, *J*=7.2 Hz, 4H, 2× CH_2 ester), 4.80 (s, 1H, C(4)-H), 7.10 (d, *J*=8.04 Hz, 2H, Ar-H), 7.21 (d, *J*=8.04 Hz, 2H, ArH), 8.81 (broad s, 1H, NH) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 14.27, 19.53, 40.12, 60.02, 102.97, 123.30, 128.92, 144.99, 146.26, 155.28, 167.19 ppm.

*2.5.1.3. Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-hydroxyphenyl)pyridine-3,5-dicarboxylate (**8c**)*

Pale yellow solid (85%, 0.294 g), Mp 174-176 °C (Lit.[46] 173-175), IR (KBr): 3600-3150,3351, 2979, 1732, 1662, 1580, 1226, 1128, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J*=7.20 Hz, 6H, 2× CH_3 ester), 2.37 (s, 6H, CH_3-2,6), 4.04-4.17 (m, 4H, 2× CH_2 ester), 4.64 (broad s, 1H, OH), 4.98 (s, 1H, C(4)-H), 5.55 (br, s, NH), 6.60 (dd, J_1=8.10 Hz, J_2=2.40 Hz, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 6.86 (d, *J*=8.10 Hz, 1H, Ar-H), 7.27 (t, *J*=8.10 Hz, 1H, Ar-H) ppm.

*2.5.1.4. Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate (**9a**)*

White solid (85%, 0.290 g), Mp 203-205 °C (Lit.[47] 202-204), IR (KBr): $\bar{\nu}$ = 3288, 3079, 2959, 1706, 1648, 1604,1488, 1381, 1214, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-7), 1.16 (s, 3H, CH_3-7), 1.22 (t, *J*=7.3 Hz, 3H, CH_3 ester), 2.13-2.36 (m, 7H, 2×CH_2, CH_3-2), 4.06 (q, *J*=7.2 Hz, 2H, CH_2 ester), 5.06 (s, 1H, C(4)-H), 6.44 (br s, 1H, NH) 7.08-7.32 (m, 5H, Ar-H) ppm.

*2.5.1.5. Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxoquinoline-3-carboxylate (**9b**)*

Yellow solid (80%, 0.308 g), Mp 237-240 °C (Lit.[48] 242-243), IR (KBr): $\bar{\nu}$ = 3295, 2959, 1699, 1605, 1517, 1482, 1345, 1218, 1073, 836, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 3H, CH_3-7), 1.16 (s, 3H, CH_3-7), 1.25 (t, *J*=7.2 Hz, 3H, CH_3 ester), 2.10-2.26 (m, 4H, CH_2-8, CH_2-6), 2.42 (s, 3H, CH_3), 4.06 (q, *J*=7.2 Hz, 2H, CH_2 ester), 5.16 (s, 1H, C(4)-H), 5.91 (s, 1H, NH), 7.48 (d, *J*=8.8 Hz, 2H, Ar-H), 8.08 (d, *J*=8.8 Hz, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21, 18.76, 26.98, 29.37, 32.62, 37.30, 40.60, 50.64, 59.14, 104.59, 110.55, 123.28, 128.97, 145.10, 146.11, 150.16, 154.72, 167.03, 195.84 ppm.

*2.5.1.6. Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(3-hydroxyphenyl)-5-oxoquinoline-3-carboxylate (**9c**)*

Brown solid (90%, 0.321 g), Mp 224-225 °C (Lit.[49] 220-222), IR (KBr): $\bar{\nu}$ = 3504, 3276, 2960, 1681, 1603, 1487, 1380, 1286, 1217, 1074, 814, 659 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ 0.87 (s, 3H, CH_3-7), 1.00 (s, 3H, CH_3-7), 1.16 (t, *J*=7.1 Hz, 3H, CH_3 ester), 2.16-2.40 (m, 4H, CH_2-8, CH_2-6), 2.40 (s, 3H, CH_3), 4.00 (q, *J*=7.1 Hz, 2H, CH_2 ester), 4.68 (s, 1H, C(4)-H), 7.39-8.08 (m, 4H, Ar-H), 8.45 (s, 1H, -OH), 8.94 (s, 1H, NH) ppm; ^{13}C

NMR (100 MHz, DMSO-d6) δ 14.2, 18.0, 26.6, 29.2, 32.1, 34.9, 50.4, 59.0, 104.1, 110.3, 114.8, 115.2, 118.1, 138.6, 143.1, 143.9, 144.1, 144.6, 149.0, 167.1, 194.3 ppm.

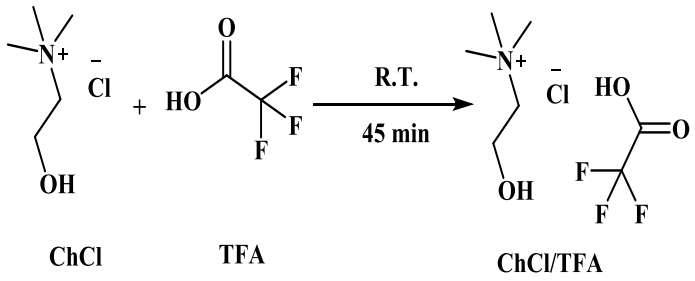
*2.5.1.8. 3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**10a**)*
Yellow solid (85%, 0.297 g), Mp 195-197 °C (Lit.[50] 191-193), IR (KBr): $\bar{\nu}$ = 3281, 1638, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 6H, 2×CH_3), 1.09 (s, 6H, 2×CH_3), 2.15 (m, 2H, CH_2) , 2.19 (m, 4H, 2×CH_2), 2.22-2.40 (m, 2H, CH_2), 5.09 (s, 1H, C(9)-H), 7.08 (s, 1H, NH), 7.09-7.34 (m, 5H, Ar-H) ppm.

*2.5.1.9. 3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**10b**)*
Yellow solid (90%, 0.355 g), Mp 290-292 °C (Lit.[51] 289-291), IR (KBr): $\bar{\nu}$ = 3377, 2957, 1645, 1608, 1550, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 6H, 2×CH_3), 1.10 (s, 6H, 2×CH_3), 2.14-2.45 (m, 8H, 4 × CH_2), 5.15 (s, 1H, C(9)-H), 6.13 (br s, 1H, NH), 7.50 (d, *J*=7.8 Hz, 2H, Ar-H), 8.07 (d, *J*=7.8 Hz, 2H, Ar-H) ppm.

*5.1.10. 3,3,6,6-tetramethyl-9-(4-methylphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**10c**)*
Yellow solid (85%, 0.309 g), Mp 263-265 °C (Lit.[51] 269-271), IR (KBr): $\bar{\nu}$ = 3275, 1673, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, 2×CH_3), 1.22 (s, 6H, 2×CH_3), 2.37 (m, 8H, 4×CH_2), 2.28 (s, 3H, CH_3), 5.48 (s, 1H, C(9)-H) , 6.79 (d, *J*=7.2 Hz, 2H, Ar-H), 6.98 (d, *J*=7.2 Hz, 2H, Ar-H), 11.91 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 26.9, 28.0, 29.4, 32.4, 33.1, 40.2, 50.8, 112.8, 127.7, 128.5, 135.0, 143.8, 149.9, 196.1 ppm.

3. Results and Discussion

Initially, in order to prepare ChCl/TFA DES (**Scheme 1**) and to determine the optimal ratio of Choline chloride and triflouroacetic acid (as hydrogen bond donor), different selected mixtures of the DES components were evaluated in terms of melting point depression with respect to the pure ingredients (**Fig. 1**). The extent of hydrogen bonding between the components considerably depends on their molar ratios. As the extent and strength of hydrogen bonding increase, the components gain more stabilization energy which



Scheme 1. Preparation of ChCl/TFA DES

serves to partially overcome the lattice energy of the solid component. A strong depression of the melting point was observed in ChCl/TFA 1.0: 1.5 molar ratios.

Melt of ChCl/TFA with the molar ratio of 1.0: 1.5 remains liquid at room temperature. 1: 1.5 mixture has no melting or freezing points. The thermal behavior of ChCl/TFA DES was determined using differential scanning calorimetry (DSC), which revealed glass transition temperature at -95 °C (**Fig. 2**).
To establish the presence of a hydrogen-bonded complex of ChCl and TFA, ^1H NMR and FTIR spectra were recorded. **Figs. 2** and **3** show the FTIR and ^1H NMR spectra of DES along with their individual components.

Comparison of the FT IR spectra shows that the FT IR spectrum of the ChCl/TFA DES nearly is an overlap of those of ChCl and TFA (**Fig. 2**). The broad band at 3600-2500 cm^{-1} is due to the stretching vibration of hydrogen bonds of OH groups of ChCl and TFA. The significant absorption bands of ChCl at 1477 (CH_2 and CH_3 scissoring mode), 1091, 950 (C-C-O asymmetric and symmetric stretching vibrations) and TFA at 1786 (stretching vibration C=O), 1178 (stretching vibration C-O) have appeared in the spectrum of ChCl/TFA DES.

The ^1H NMR spectrum of D_2O solution of the DES revealed upfield shifts (about 0.43 ppm) for protons of methyl and two different methylenes of choline chloride as compared to those obtained for choline chloride in D_2O solution. The upfield shifts have been reported for the protons of ChCl in D_2O solution of Itaconic acid (IA)/Choline chloride (CC) DES [52]. The peaks of exchangeable hydrogen atoms, O-H and COOH, disappeared owing to D_2O. The residual HDO signal of solvent is observed at 4.7 ppm.

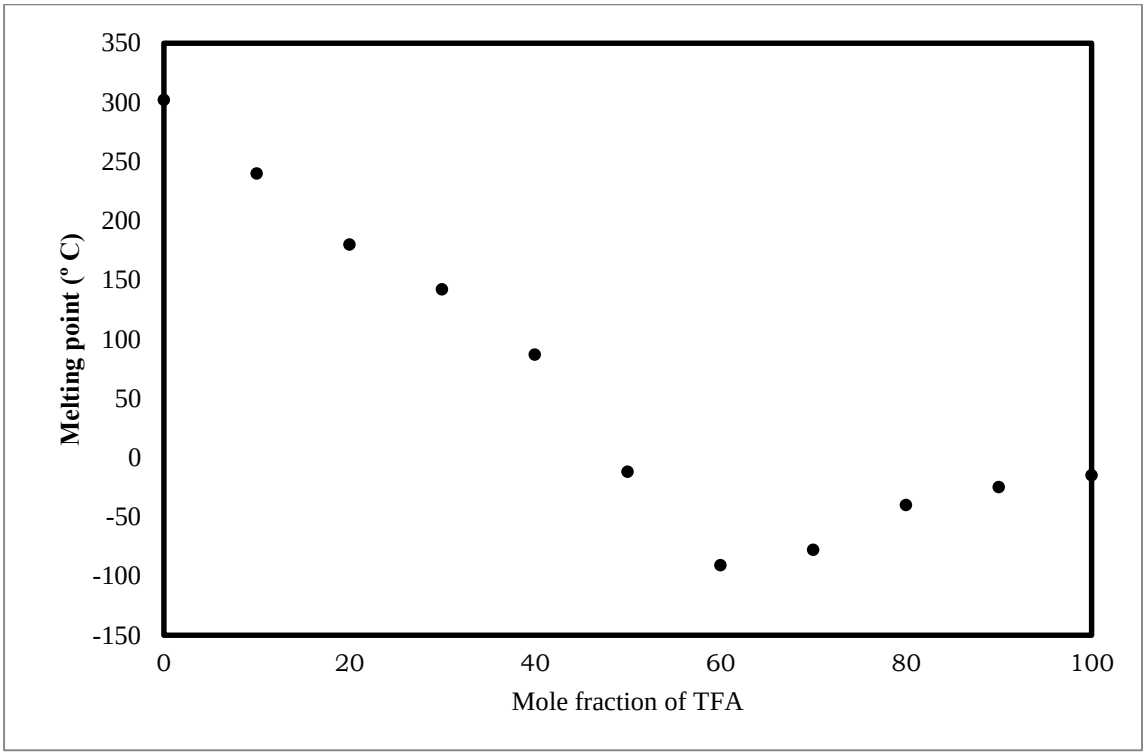


Fig. 1. Phase diagram of ChCl-TFA mixtures. Points on graph indicate melting temperature of mixture of ChCl-TFA in different molar ratios.

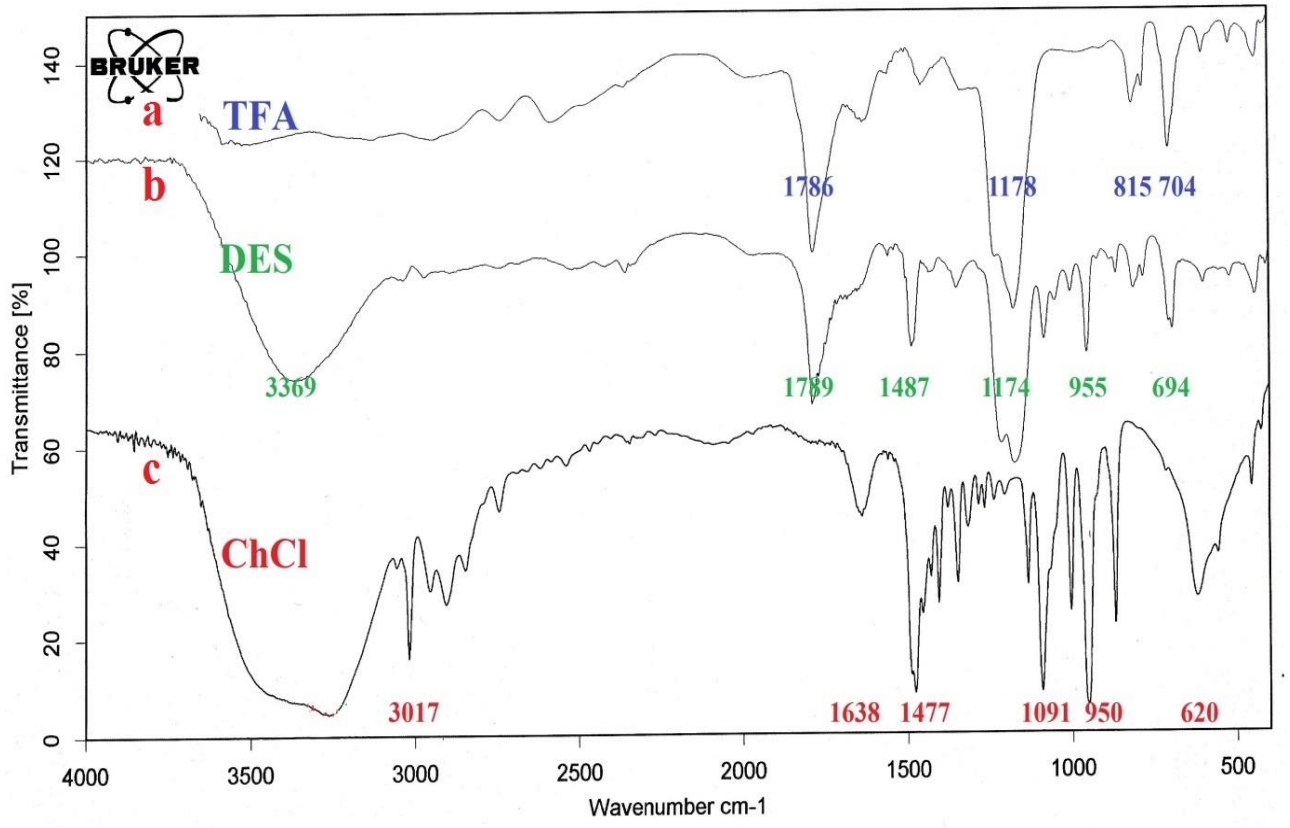


Fig. 2. FT IR spectra of (a) TFA, (b) ChCl/TFA DES, (c) ChCl.

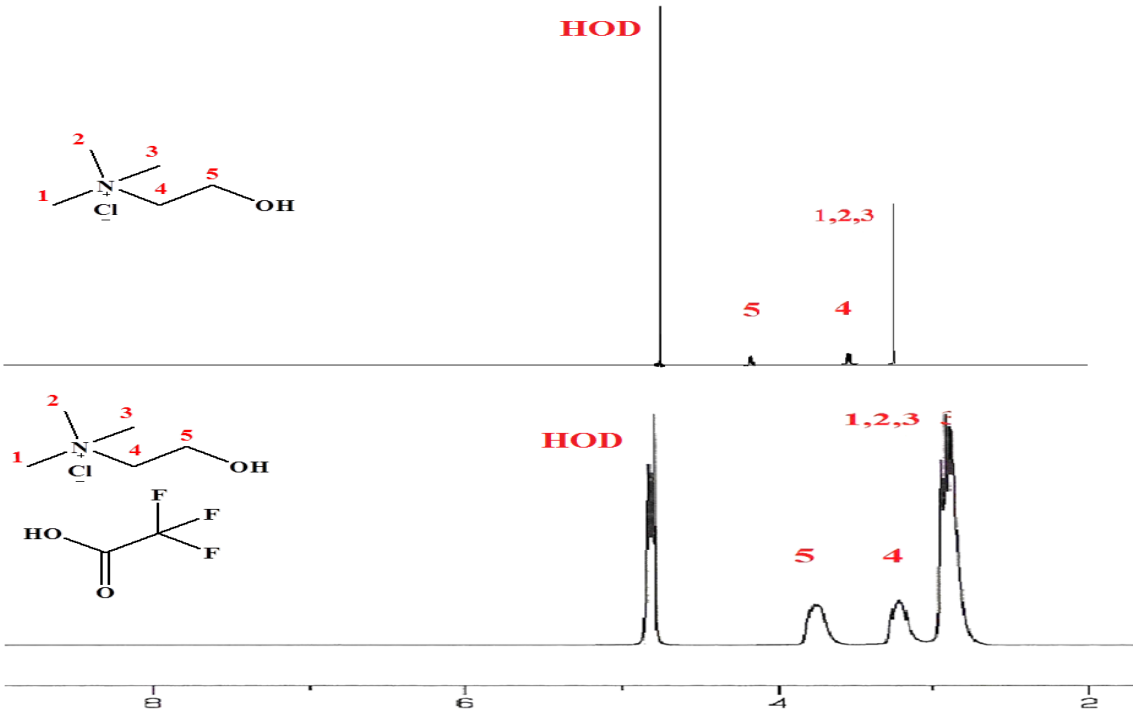


Fig. 3. ^{1}H NMR spectra of 1 : 1.5 ChCl/TFA solution in D_2O.

Furthermore, physical properties of the most stable mixture of ChCl/TFA such as viscosity and density were determined (**Table 1**).Next, we investigated the application of this novel ChCl/TFA DES as reaction medium as well as catalyst for some multicomponent reactions. In order to optimize the Biginelli reaction in ChCl/TFA DES, the reaction between benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), and urea (1.25 mmol) was selected as a model reaction in different temperatures. It was observed that the yield of reaction increases by raising the temperature from room temperature to 70° C, but further increase in temperature to 90 °C did not show any effect on the yield of the product. The results in two different temperatures (25 and 70 °C) were shown in **Table 2**.

Table 1. The physicochemical parameters of ChCl/TFA DES

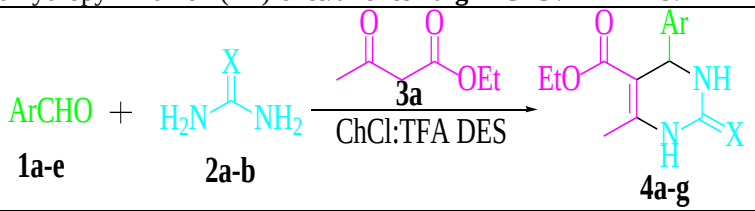
Molar ratio (ChCl:TFA)	1:1.5
M_w [b](g mol^{-1})	124.26
Glass transition temperature, T_g (^{o}C)	-95
Density[a], ρ (g cm^{-3})	1.284106
Viscosity[a], η (mPa s)	5836
Sound speed[a], u (m s^{-1})	1425.21

a) determined at 25 ^{o}C, [b] $M_{w\,DES} = x_{ChCl}.M_{w\,ChCl} + x_{TFA}.M_{w\,TFA}$, x_{ChCl}: molar fraction of choline chloride, $M_{w\,ChCl}$: molecular waight of Choline chloride, and x_{TFA}: molar fraction of triflouroacetic acid, $M_{w\,TFA}$: molecular waight of triflouroacetic acid.

With these findings in hand, we used ChCl/TFA DES in the synthesis of diverse derivatives of 3,4-dihydropyrimidin-2(1H)-ones/thiones *via* Biginelli reaction under the optimal conditions using aromatic aldehydes, urea/thiourea, and ethyl acetoacetate (**Table 2**). As indicated in **Table 2**, aromatic aldehydes containing both electron-donating and electron-withdrawing groups were well tolerated. Notably, reactions with urea in comparison with thiourea need a short reaction time; which can be explained by greater nucleophilicity of urea. Also, to exhibit scope of this methodology and to synthesize dihydropyrimidinone derivatives, we performed Biginelli-like cyclocondensation of cycloalkanones (cyclopentanone **5a** and cyclohexanone **5b**), urea, and aromatic aldehydes at 70 °C in ChCl/TFA DES. The 7-arylidene-3,4,6,7-tetrahydro-4-aryl-1H-cyclopenta[d]pyrimidin-2(5H)-ones, and 8-arylidene-3,4,5,6,7,8-hexahydro-4-arylquinazolin-2(1H)-ones (**6a-d**) were obtained in high yields and short reaction time (**Table 3**). As the results indicated in Table 3, reaction times with cyclohexanone are longer than that of cyclopentanone, because of the lower reactivity and more crowded conformation of cyclohexanone.

The first step of this reaction is cross-aldol condensation of arylaldehyde with cycloalkanone which affords the corresponding α,α′-bis(substituted benzylidene)cycloalkanone. Subsequently, a Michael addition of the urea to benzylidene derivative followed

Table 2. Synthesis of 3,4-dihydropyrimidine-2(1H)-ones/thiones **4a-g** in ChCl/TFA DES.



Entry	Ar	X	product	R.T.		70 °C		m.p. (°C)	
				Time (min)	Yield [a] (%)	Time (min)	Yield [a] (%)	Found	Reported
1	C_6H_5	O	**4a**	37	90	12	96	196-198	200-201 [38]
2	4-$O_2NC_6H_4$	O	**4b**	40	94	13	95	210-212	210 [39]
3	3-$MeOC_6H_4$	O	**4c**	35	88	12	92	200-202	205-207 [38]
4	4-MeC_6H_4	O	**4d**	34	85	11	94	210-213	215-217 [43]
5	2-Furyl	O	**4e**	38	80	10	85	200-203	205-206 [39]
6	C_6H_5	S	**4f**	70	85	24	94	202-204	204-207 [25]
7	3-$O_2NC_6H_4$	S	**4g**	75	92	25	90	203-205	206-209 [38]
8	4-$MeOC_6H_4$	S	**4h**	70	90	20	90	153-154	150-152
9	4-Cl C_6H_4	S	**4i**	55	85	24	90	191-192	192-195
10	4-Cl C_6H_4	O	**4j**	45	87	12	90	209-210	213-215 [38]
11	2-ClC_6H_4	O	**4k**	40	85	13	92	223-224	224-225 [38]
12	3-$O_2NC_6H_4$	O	**4l**	45	90	15	95	227-228	226-227
13	4-$MeOC_6H_4$	O	**4m**	30	90	10	95	200-201	201-203
14	2-$MeOC_6H_4$	O	**4n**	35	85	15	90	260-262	262
15	4-$Me_2NC_6H_4$	O	**4o**	30	90	15	90	257-258	256-258

a) Isolated yields, b) All the products are known and were identified by comparison of their IR and NMR spectra, or melting points with those of authentic samples.

by cyclization and elimination of water produces pyrimidinone derivatives **6a-d**.

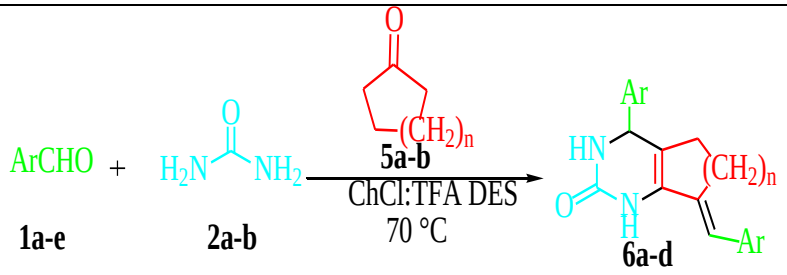
Encouraged by the good results, we also decided to do Hantzsch reaction in the novel ChCl/TFA DES medium. The reaction of methylene active compounds (ethyl acetoacetate and dimedone), arylaldehydes and ammonium acetate in ChCl/TFA DES were performed at 70 ° C, both the symmetrical and unsymmetrical Hantzsch ptoducts were obtained in high yields and short reaction times (**Table 4**).

Recovery and reusability of DES were studied for the preparation of **4a**, **6a** and **10b** compounds under optimized conditions. At the end of the reactions, the DES can be easily recovered (by precipitation) by addition of water to the reaction mixture. After filtration, the water phase was evaporated under reduced pressure and washed with ethyl acetate and used for the next run. The results are presented in **Fig. 4**. In fact, the reactions are very clean, and no side product was obtained in any run.

A reaction mechanism is proposed in **Scheme 2**. It seems that the DES can play a dual role, at first the carbonyl group of aryl aldehyde is activated by the acetate section of catalyst, and with addaition of urea, imonium ion derivative is formed. On the other hand, DES facilities the formation of the enol tautomer of ethyl acetoacetate, in the following with interaction of imonium ion with enol tautomer and the cyclic reaction, the product is formed. A similar mechanism for the Hansch reaction is given in **Scheme 3**.

In order to show the efficiency of this method, **Table 5** compares our results (time, yield, reaction conditions) with some of other methods for the synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1H) ones by ferric hydrogen sulfate (entry 3-4), Tangstophosphoric acid as bulk and supported Catalysts (entry 5-6), hydrogen sulfate ionic liquid immobilized silica (entry 7), Imidazolium-based phosphinite ionic liquidas (entry 8), Silvertangstophosphate (entry 9) and Indium triflate (entry10). As shown in **Table 5**, our method is simpler, more efficient, and uses no solvent for the synthesis of dihydropyrimidinone derivatives. Although, there are many suitable ways and catalysts to prepare the Biginelli and Hantzsch reactions with excellent yields, in this work we used a new deep eutectic solvent (DES) as a catalyst and solvent in Biginelli, Biginelli-like, and Hantzsch reactions. Compared with the classical Biginelli and Hantzsch reaction conditions, this new method has the advantage

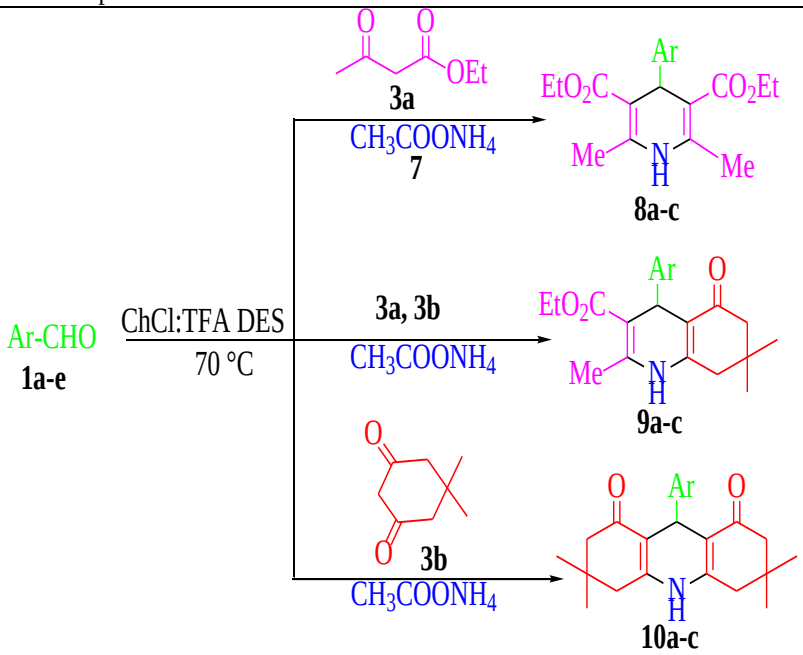
Table 3. Biginelli-like cyclocondensations of cycloalkanones, urea and aromatic aldehydes in ChCl/TFA DES.



Entry	Ar	n	product	Time (min)	Yield[a] (%)	m.p. (°C)	
						Found	Reported
1	4-BrC_6H_4	1	**6a**	12	94	224-226	217-220[37]
2	3-$O_2NC_6H_4$	1	**6b**	10	92	230-232	227-230[37]
3	C_6H_4	1	**6c**	12	90	207-208	207-210[37]
4	2-ClC_6H_4	1	**6d**	10	90	220-221	219-222[37]
5	4-ClC_6H_4	1	**6e**	15	95	209-2011	208-2011[37]
6	2-$MeOC_6H_4$	1	**6f**	12	90	228-230	227-230[37]
7	4-$MeOC_6H_4$	1	**6g**	15	92	211-213	212-215[37]
8	4-FC_6H_4	1	**6h**	15	90	215-216	214-217[37]
9	4-BrC_6H_4	2	**6i**	35	88	268-270	273-275[38]
10	3-$O_2NC_6H_4$	2	**6j**	30	90	202-205	205-207[44]
11	C_6H_5	2	**6k**	35	90	195-197	196-198[44]
12	2-$MeOC_6H_4$	2	**6l**	30	88	201-203	200-202[44]
13	4-$MeOC_6H_4$	2	**6m**	25	85	203-204	204-205[44]
14	4-ClC_6H_4	2	**6n**	35	80	203-205	204-205[44]
15	2-$O_2NC_6H_4$	2	**6o**	30	85	206-207	205-207[44]
16	4-FC_6H_4	2	**6p**	35	90	205-206	205-207[44]

a) Isolated yields, b)All the products are known and were identified by comparison of their melting points with those of authentic samples

Table 4 Synthesis of Hantzsch products in ChCl/TFA DES.



Entry	Ar	Product	Time (min)	Yield[a] (%)	m.p. (°C)	
					Found	Reported
1	C_6H_5	**8a**	8	90	158-160	156-158 [45]
2	4-$O_2NC_6H_4$	**8b**	5	95	132-134	130-132 [45]
3	3-HOC_6H_4	**8c**	5	85	174-176	172-175 [46]
4	C_6H_5	**9a**	10	85	203-205	202-204 [47]
5	4-$O_2NC_6H_4$	**9b**	5	80	237-240	242-243 [48]
6	3-HOC_6H_4	**9c**	8	90	224-225	220-222 [49]
7	C_6H_5	**10a**	6	85	195-197	191-193 [50]
8	4-$O_2NC_6H_4$	**10b**	7	90	290-292	286-289 [51]
9	4-MeC_6H_4	**10c**	10	85	263-265	269-271 [51]

a) Isolated yields, b) All the products are known and were identified by comparison of their melting points with those of authentic samples.

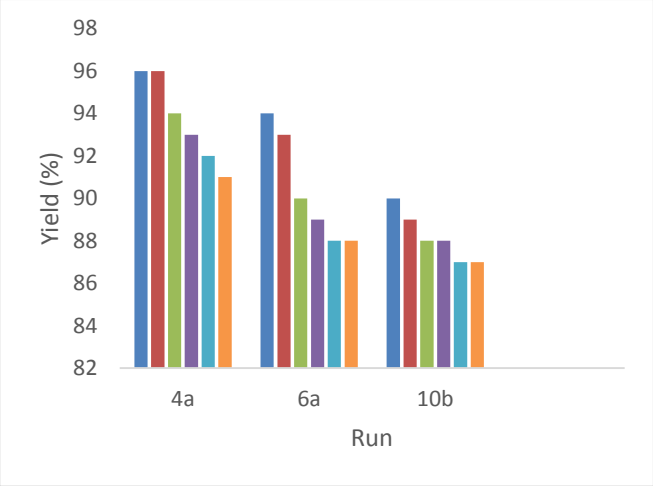
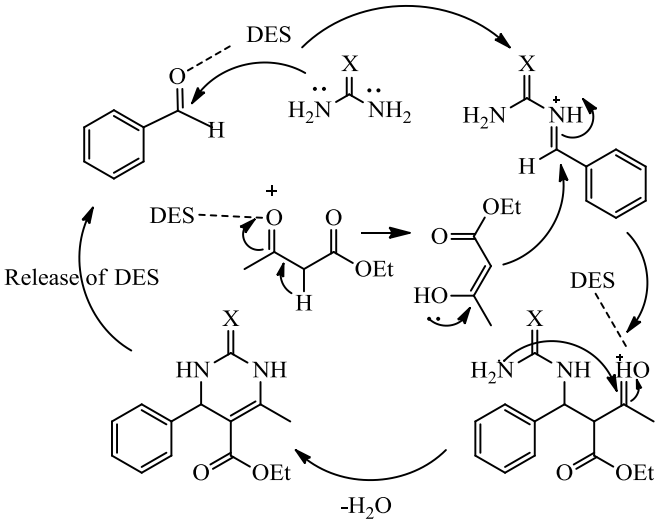
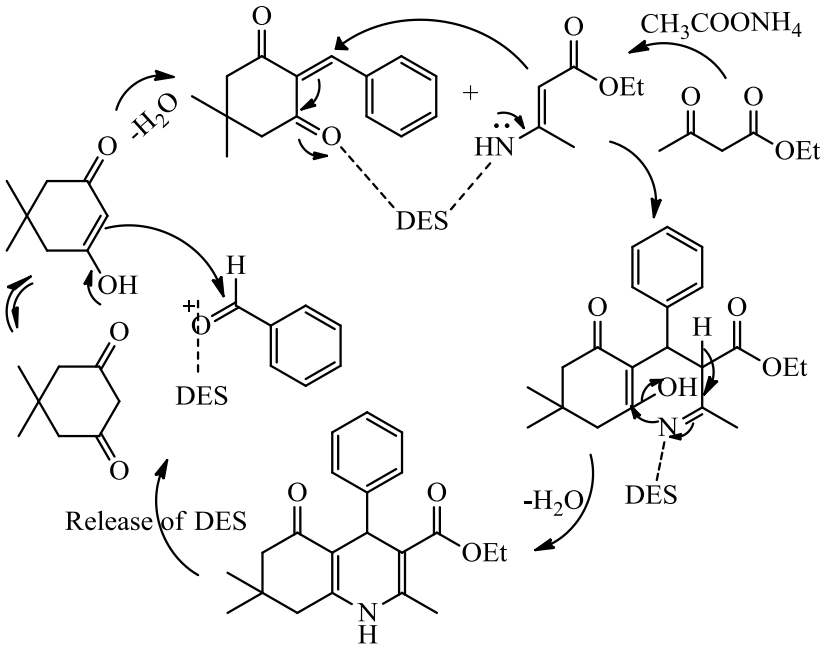


Fig. 4. Reusability of the DES in the model reaction of 4a, 6a and 10b



Scheme 2. Proposed mechanism for one-pot synthesis of 3,4-DHPMs derivatives in the presence of DES



Scheme 3. Proposed mechanism for preparation of dihydropyridine derivatives through the Hansch reaction in the presence of DES

of good to excellent yields, short reaction time and easy work-up, and it does not require additional catalysts and organic solvents. The DES is reusable and can be applied several times without any decrease in the yield of the reactions.

Table 5 The Comparison of Efficiency of present method (1,2) with other reported methods for synthesis of 3,4-DHPMs derivatives by (2-10) compounds

Row	Catalyst	Condition	Yield (%)	Time (min)	Ref.
1	ChCl/TFA DES	Only DES/R.T.	80-90	30-55	Table 2
2	ChCl/TFA DES	Only DES/70ºC	90-95	10-24	Table 2
3	$Fe(HSO_4)_3$	CH_3CN/Reflux	80-95	90-120	[53]
4	$Fe(HSO_4)_3$	Solvent-free/100º C	80-95	90-120	[53]
5	$H_3PW_{12}O_{40}$	Solvent-free/80ºC	86-93	60-90	[54]
6	SiO_2–$H_3PW_{12}O_{40}$	Solvent-free/80ºC	87-93	120	[54]
7	IL-HSO4	EtOH/R.T.	80-95	30-55	[55]
8	IL-PPh2	Solvent-free/100º C	88-94	90-180	[56]
9	$Ag_3PW_{12}O_{40}$	EtOH/ Reflux	87–96	150-240	[57]
10	$In(OTf)_3$	EtOH, Reflux/N_2	82-97	240-810	[58]

4. Conclusions

In conclusion, we prepared the eutectic mixture of choline chloride (ChCl) and triflouroacetic acid (TFA) for the first time. Then, we have developed a simple and facile practical method using the ChCl/TFA DES as a dual catalyst and reaction media, for easy access to a wide range of pharmaceutically attractive functionalized DHPs and DHPMs. Mild reaction conditions, excellent yields, short reaction times, simple separation procedures, clean reaction profiles, high energy- and atom-economy are the key advantages of the present methodology.

Acknowledgements

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