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RESEARCH ARTICLE

Green and Facile Synthesis of Pyrimidine Derivatives using Chloride Chloride-urea Mixture as a Deep Eutectic Solvent or Cerium (IV) Ammonium Nitrate

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Abstract: An efficient and facile synthesis of substituted pyrimidine derivatives through Biginelli type reaction was achieved in high yields *via* one-pot reaction of aromatic aldehydes, active methylene compounds and urea or thiourea in the presence of choline chloride-urea mixture as a deep eutectic solvent or cerium (IV) ammonium nitrate (CAN) as a catalyst at different conditions. The reaction was carried out using different ratio of CAN in different solvents to determine the optimum conditions. In addition, 2-mercapto-6-oxo-4-(thiophen-2-yl)-1,6-dihydropyrimidine-5-carbonitrile was employed in the synthesis of pyrimidinylhydrazide and its corresponding hydrazone. The structural formula of all derivatives was confirmed and characterized by their elemental analyses and spectral data (IR, MS, ^{1}H NMR, ^{13}C NMR).

Keywords: Pyrimidine; deep eutectic solvent; cerium (IV) ammonium nitrate; hydrazine, catalyst, active methylene, hydrogen.

1. INTRODUCTION

In recent years, deep eutectic solvents (DESs) have attracted great attention as green solvents in many organic reactions and transformations [1-7]. DESs can be easily formulated *via* hydrogen bonding between two components, the first is hydrogen bond donor which can be acid [8], alcohol [9, 10] carbohydrate [11] or amide [12, 13] and the second is hydrogen bond acceptor such as quaternary ammonium salt [13, 14]. Non-flammability, high thermal stability and low volatility of DESs promote their uses as versatile alternatives than conventional solvents [15]. DESs have additional advantages as being inexpensive, non-toxic, biodegradable and recyclable green solvents. On the other hand, cerium (IV) ammonium nitrate (CAN) is one of the most important catalysts that are used in recent years as nontoxic, cheap and commercially available catalysts in organic synthesis [16-18]. CAN is characterized also with good solubility in different organic media, easy handling and eco-friendly catalyst [19].

In addition, pyrimidine derivatives are an important group of heterocyclic compounds that possess a wide range of pharmacological properties, which include their uses as antimicrobial [20-26], anticancer [27-34], antitumor [35], antioxidant [36], anti-inflammatory [37, 38] and antiviral agents [39].

In view of these observations and in continuation of our ongoing interest in the design of bio-active heterocyclic molecules [40-45], the present work involves a green one-pot synthesis of pyrimidine derivatives using CAN as a catalyst or choline chloride-urea mixture as a deep eutectic solvent. Comparative studies were discussed also between the traditional procedures and the ones obtained by green chemistry conditions.

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2. RESULTS AND DISCUSSION

Herein, we report an effective and facile methods for the synthesis of pyrimidine derivatives through multicomponent reaction involving aromatic aldehydes, active methylene compounds and urea or thiourea in the presence of choline chloride-urea mixture as a deep eutectic solvent or cerium (IV) ammonium nitrate (CAN) as a catalyst.

The first method involves the reaction of thiophene-2-carbaldehyde with ethyl acetoacetate and urea or thiourea using choline chloride-urea mixture (1:2) to afford pyrimidines **1a,b** in good yield 82-80 %. In addition, the reaction was performed in many DES systems, such as choline chloride-glycerol and choline chloride-glucose, but unfortunately, they gave unpromising yields. In an attempt to enhance the yield of the produced pyrimidines in choline chloride-urea, we added the base triethylamine (TEA), and isolated excellent yield of the product 93% in shorter reaction time (Scheme **1**). The results are consistent with the previously reported data [46]

The reaction probably takes place via the following mechanism (Fig. **1**).

The second method involves the synthesis of pyrimidine derivatives using CAN as a catalyst in different media. Initially, the reaction of thiophene-2-carbaldehyde with ethyl acetoacetate and urea in the presence of CAN to synthesize pyrimidine **1a** (Scheme **2**) was selected as a model reaction to investigate the effect of solvent and solvent-free conditions as shown in Table **2**. Lower yield and longer reaction time were observed during the use of methanol and water (entry 2, 4) while ethanol and ethanol/water mixture (1:1) showed higher yields (entry 1, 3). In addition, grinding method under free solvent offers high yield of pyrimidine **1a** in shorter time. It is clear from the results depicted in Table **2** that ethanol was

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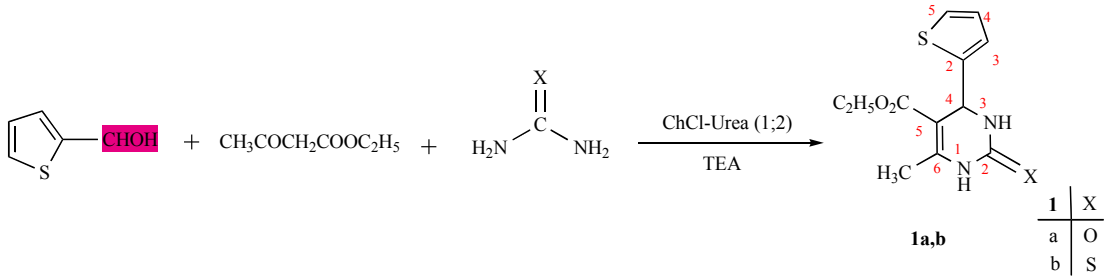


Scheme 1. Synthesis of pyrimidines **1a,b** using choline chloride-urea mixture (ChCl-Urea, 1:2).

Table 1. Synthesis of pyrimidines 1a,b using choline chloride-urea mixture at 70 °C.

Entry	Product	Reaction Media	Time (hour)	Yield (%)
1	1a	-	10	82
2	1b	-	9	80
3	1a	TEA	5	93
4	1b	TEA	6	93

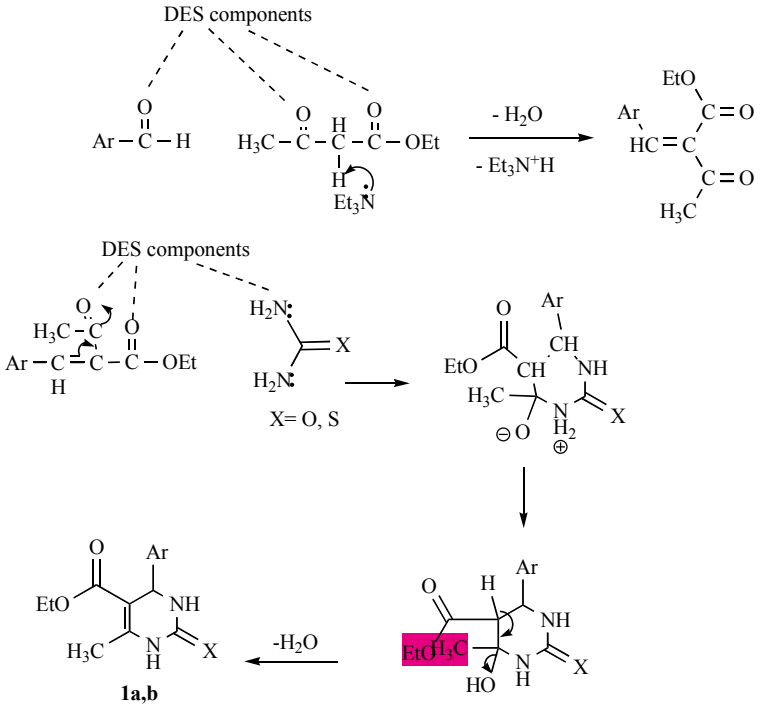
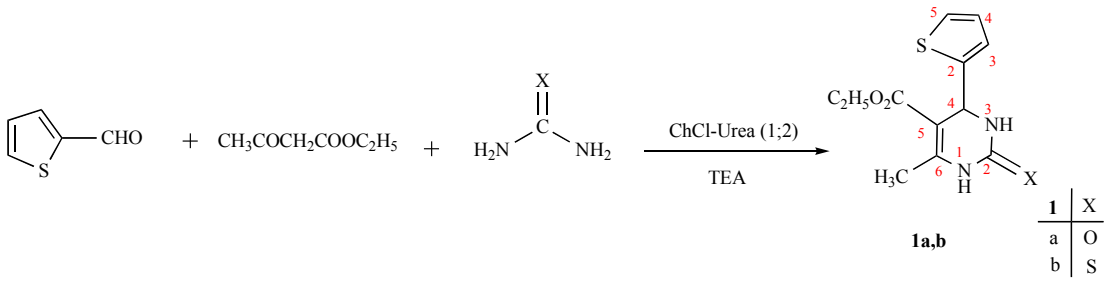


Fig. (1). Plausible mechanism for formation of pyrimidines **1a,b**.

the most effective solvent in isolation of higher yield 94% of pyrimidine **1a**.

On the other hand, the reaction was carried out using a different ratio of CAN(0.0001, 0.0005, 0.001, 0.003 mol) in ethanol. The results revealed that 0.003 mol of the catalyst gave the highest yield (94 %) while other ratios offer lower yields.

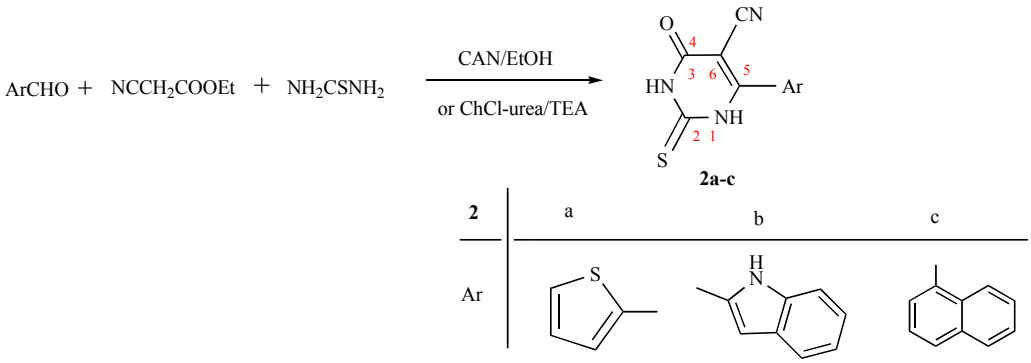
From these results and in order to generalize this one-pot catalyzed synthesis *via* the two methods, we prepare a series of pyrimidine derivatives 2a-c using ethyl cyanoacetate as an active methylene compound and variety of aromatic aldehydes as thiophene-2-carboxyaldehyde, indol-2-carboxyaldehyde and naphthalene-1-carboxyaldehyde in addition to thiourea using CAN as a catalyst in ethanol, (Scheme **3**). The reaction was carried also using choline chloride-urea mixture (1:2) as a deep eutectic solvent. The chemical structures of pyrimidines **2a-c** were elucidated on the basis of their spectral analyses. IR spectra exhibited absorption bands at 3430-3210, 2214-2226, 1685-1668 cm^{-1} corresponding to functional groups NH, C≡N and CO respectively. ^{1}H NMR spectra also showed characteristic signals of NH protons. To confirm the obtained results for the synthesis of pyrimidine products, the reaction was repeated and performed *via* conventional synthesis using potassium carbonate in ethanol. The spectral analyses and melting points of products are consistent with all synthetic pathways; comparative analysis of the results are shown in Table **3**.



Scheme 2. Synthesis of ethyl 4-methyl-2-oxo-6-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(1a)** in the presence of CAN.

Table 2. CAN catalysed synthesis of ethyl 4-methyl-2-oxo-6-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a) using various solvents and solvent free conditions at 80 °C.

Entry	Solvent	Time (h)	Yield (%)
1	EtOH	3.5	94
2	H_2O	5	80
3	EtOH + H_2O (1:1)	5	85
4	MeOH	6	79
5	Grinding	0.5	86



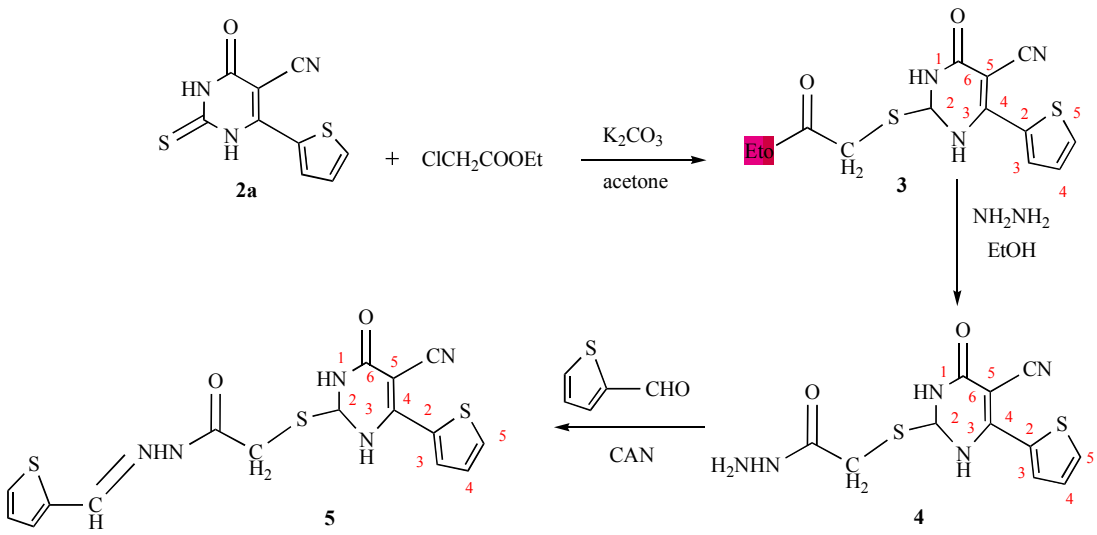
Scheme 3. Synthesis of pyrimidines **2a-c**.

Table 3. Comparative studies for synthesis of pyrimidines 2a-c *via* different conditions.

Entry	Product	Reaction Conditions	Reaction Time (hour)	Yield %
1	2a	CAN+ EtOH	5	93
2	2b	CAN+ EtOH	6	92
3	2c	CAN+ EtOH	5	90
4	2a	ChCl-urea (1:2)	7	91
5	2b	ChCl-urea (1:2)	8	90
6	2c	ChCl-urea (1:2)	7	89
7	2a	K_2CO_3 + EtOH	5	80
8	2b	K_2CO_3 + EtOH	6	78
9	2c	K_2CO_3 + EtOH	6	75

From data given in Table **3**, we noticed that the reaction using cerium (IV) ammonium nitrate or choline chloride-urea mixture offered higher yields of the products in comparison with their synthesis using potassium carbonate.

On the other hand, pyrimidine derivative **2a** was used as a reactive key precursor to construct a series of new heterocyclic molecules. Thus, pyrimidine **2a** reacted with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dry acetone as a



Scheme 4. Synthesis of hydrazone **5**.

polar aprotic solvent to give *S*-alkylated product, Ethyl 2-(5-cyano - 6-(4,5-dihydrothiophen- 2-yl) – 4–oxo -1,2,3,4-tetrahydropyrimidin - 2 -ylthio)acetate **(3)** [47]. Hydrazinolysis of the ester **3** *via* nucleophilic attack by hydrazine hydrate on the electron-deficient carbonyl carbon formed the corresponding hydrazide **4**. The latter reacted with thiophene-2-carbaldehyde to form the corresponding hydrazone **5** (Scheme **4**).

3. EXPERIMENTAL

The chemical reagents were purchased from Sigma-Aldrich (St. Louis,MO). Solvents were commercially available at El-Nasr Chemicals Co. (Egypt) in analytical grade and were used without further purification. Thin-layer chromatography was conducted on precoated silica gel polyester sheets (Kieselgel 60 F254, 0.20 mm, Merck, Kenilworth, NJ).

Melting points were measured using an electro-thermal digital apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using Buck scientific model 500 IR spectrophotometer. The proton NMR spectra were recorded in DMSO-d6 as a solvent at 400 MHz, on a Varian Gemini NMR spectrophotometer using TMS as an internal standard, the chemical shifts were reported as parts per million (ppm). Microanalyses were performed at the micro-analytical center, Cairo University and Mansoura University.

General procedures for synthesis of pyrimidines 1a,b:

3.1. First Method

To a mixture of 0.01 mol of thiophene-2-carboxaldehyde (1.1 g), ethyl acetoacetate (1.3 g, 0.01 mol) and urea (0.6 g, 0.01 mol) or thiourea (0.8 g, 0.01 mol) in choline chloride-urea mixture (2 mL) [prepared by warming a mixture of choline chloride and urea 1:2] [8], few drops of TEA were added. The reaction mixture was refluxed for 5-6 hours. After cooling, the mixture was poured gradually on crushed ice and the solid separated was filtered off, washed three times with distilled water and crystallized with ethanol to give **1a,b**.

3.2. Second Method

A mixture of 0.01 mol of thiophene-2-carboxyaldehyde (1.12 g), ethyl acetoacetate (1.3 g) and urea (0.6 g, 0.01 mol) or thiourea (0.8 g, 0.01 mol) and cerium (IV) ammonium nitrate (1.6 g, 0.003 mol) in absolute ethanol (20 mL) was refluxed for 3.5 hours. The reaction mixture was poured gradually on crushed ice and the solid separated was filtered off, washed and crystallized with ethanol to give **1a,b**.

3.2.1. Ethyl 4-methyl-2-oxo-6-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a)

Yield 93 %; M.p. 208-210° C; ^{13}CNMR (DMSO-d_6, δ ppm):166.2 (C14), 150.9 (C10), 146.3 (C8), 138.2 (C1), 127.4 (C3), 126.2 (C2), 125.1 (C4), 105.4 (C7), 60.6 (C18), 53.2 (C6), 17.1 (C13), 15.2 (C17); ^{1}HNMR (DMSO-d_6, δ ppm): 1.19 (t, J = 7.2, 3H, CH_2CH_3), 2.22 (s, 3H, CH_3), 4.09 (q, J = 7.2, 2H, CH_2CH_3), 5.41 (s, 1H, CH), 6.89-7.35 (m, 3H, Ar-H), 7.87, 9.27 (2s, 2H, 2 NH, exchangeable);MS; m/z: 266.07 (M^+); IR (KBr, ν cm^{-1}): 3236-3112 (2 NH), 1725, 1661 (2 CO); Anal. calcd. for $C_{12}H_{14}N_2O_3S$ (266.32): C, 54.12; H, 10.52; N, 5.30; Found: C, 54.09; H, 10.48; N, 5.25.

3.2.2. Ethyl-6-methyl-4-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b)

Yield 93 %; M.p. 188-190° C; ^{13}CNMR (DMSO-d_6, δ ppm):179.2 (C10), 166.1 (C14), 160.8 (C8), 138.2 (C1), 126.4 (C2), 126.1 (C3), 125.2 (C4), 103.2(C7), 61.2 (C18), 58.0(C6), 18.7 (C13), 14.6 (C17); ^{1}HNMR (DMSO-d_6, δ ppm): 1.16 (t, J = 7.2, 3H, CH_2CH_3), 2.21 (s, 3H, CH_3), 4.07 (q, J = 7.2, 2H, CH_2CH_3), 5. 42 (s, 1H, CH), 6.88-7.35 (m, 3H, Ar-H), 7.86, 9.27 (2s, 2H, 2 NH, exchangeable);IR (KBr, ν cm^{-1}): 3446-3241 (2 NH), 1727, 1670 (2 CO);MS;m/z: 282.05(M^+); Anal. calcd. for $C_{12}H_{14}N_2O_2S_2$(282.38): C, 51.04; H, 5.00; N, 9.92; Found: C, 50.93; H, 4.94; N, 9.88.

3.2.3. General Procedures for the Synthesis of 2a-c

3.2.3.1. First Method

A mixture of 0.01 molof aromatic aldehydes namely, thiophene-2-carboxaldehyde (1.1 g), indole-3-carboxaldehyde (1.5 g, 0.01) and 1-naphthaldehyde (1.6 g), ethyl cyanoacetate (1.13 g), thiourea (0.8 g, 0.01 mol) and cerium (IV) ammonium nitrate (1.6 g, 0.003 mol) in absolute ethanol (20 mL) was refluxed for 5-6 h. The precipitated solid was filtered off, washed and crystallized with ethanol to give **2a-c** respectively.

3.2.3.2. Second Method

A mixture of 0.01 mol of aromatic aldehydes namely, thiophene-2-carboxaldehyde (1.1 g), indole-3-carboxaldehyde (1.5 g) and 1-naphthaldehyde (1.6 g, 0.01 mol), ethyl cyanoacetate (1.1 g) and thiourea (0.8 g, 0.01 mol) in choline chloride-urea mixture (2 mL) was refluxed for 7-8 h. After cooling, the reaction mixture was poured gradually onto crushed ice and the solid separated was filtered off, washed three times with distilled water and crystallized with ethanol to give **2a-c** respectively.

3.2.3.3. Third Method

A mixture of 0.01 mol of ethyl cyanoacetate (1.13 g), aromatic aldehydes namely, thiophene-2-carbaldehyde (1.1 g), indole-3-carboxaldehyde (1.5 g) and 1-naphthaldehyde (1.6 g) and thiourea (0.8 g, 0.01 mol) in ethanol (20 mL) containing potassium carbonate (1.4 g, 0.01 mol) was refluxed for 5-6 h. The potassium salt of product, which was precipitated during the reaction, was collected and washed with ethanol and tetrahydrofuran. The crude salt was stirred in water at approximately 80° C; stirring was continued until the clear solution was obtained. After cooling, the solution was acidified by acetic acid, and stirring was continued for 30 min. The deposited crystals thus formed were collected and washed well with water and dried in air and crystallized to give pure products **2a-c**.

4-Oxo-6-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (2a).

Yield 93 %; M.p. 180-182°C;^{13}CNMR (DMSO-d_6, δ ppm):176.1 (C1), 174.2 (C5), 166.5 (C3), 136.1 (C12), 130.2 (C9), 128.1 (C10), 127 (C11), 115.2 (C14), 80.1 (C2); ^{1}HNMR (DMSO-d_6, δ ppm):6.97-8.03 (m, 3H, Ar-H), 7.23, 9.52 (2s, 2H, 2NH, exchangeable); **IR**(KBr, ν cm^{-1}): 3350-3210 cm^{-1} (NH)**,** 2214 (C≡N),1673 (CO)**;**MS; m/z: 234.99(M^{+}); Anal. calcd. for $C_9H_5N_3OS_2$(235.28): C, 45.95; H, 2.14; N, 17.86; Found: C, 45.90; H, 2.09; N, 17.81.

3.2.4. 6-(1H-indol-2-yl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (2b)

Yield 92 %; M.p. 226-228° C;^{13}CNMR (DMSO-d_6, δ ppm): 176.1(C1), 174.5 (C5), 166.1 (C3), 130.5(C12), 127.6(C11), 122.1(C9), 121.2(C16), 120.1(C14), 119.2(C15), 115.1(C18), 110.5(C17), 100.5(C10), 79.1(C2);^{1}HNMR (DMSO-d_6, δ ppm):7.23-8.55 (m, 5H, Ar-H), 9.45, 12.52 (3s, 3H, 3NH, exchangeable);IR (KBr, ν cm^{-1}): 3431-3272 (NH), 3050 (CH aromatic), 2220 (C≡N), 1684 (CO);MS; m/z: 268.04(M^{+});Anal. calcd. for $C_{13}H_8N_4OS$ (268.29): C, 58.20; H, 3.01; N, 20.88; Found: C, 58.15; H, 2.95; N, 20.81.

3.2.5. 6-(Naphthalen-2-yl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (2c)

Yield 90 %; M.p. 190-192° C; ^{13}CNMR (DMSO-d_6, δ ppm): 174.4 (C5), 168.1(C1), 165.7(C3), 135.1(C14), 133.2(C12), 130.3(C13), 128.2(C15), 127.8(C11), 126.1(C10), 126(C17), 125.6(C16), 124.2(C18), 121.5 (C9), 115.2(C19),73.5 (C2);^{1}H NMR (DMSO-d_6, δ ppm):7.60-8.17 (m, 7H, Ar-H), 4.02, 8.98 (2s, 2H, 2NH, exchangeable); IR (KBr, ν, cm^{-1}): 3438-3265 (NH), 3052 (CH aromatic), 2226 (C≡N)**,** 1684 (CO);MS; m/z: 279.05(M^{+});Anal. calcd. for $C_{15}H_9N_3OS$ (279.32): C, 64.50; H, 3.25; N, 15.04; Found: C, 64.45; H, 3.19; N, 14.95.

3.2.6. Ethyl 2-(5-cyano -6-(4,5-dihydrothiophen- 2-yl) – 4–oxo - 1,2,3,4-tetrahydropyrimidin - 2 -ylthio)acetate (3)

A mixture of 0.01 mol of compound **2a** (2.4 g) and ethyl chloroacetate (1.2 g) in dry acetone (25 ml) containing anhydrous potassium carbonate (1.4 g, 0.01 mol) was heated under reflux on a water bath for 6 h. During reflux, the temperature was maintained around 60 - 65° C. The white coloured potassium salt of product obtained was dissolved in hot water. After cooling, the solution was acidified by dilute hydrochloric acid to precipitate the product. The product was filtered and washed with water. The crude product was dried and recrystallized from ethanol to obtain pure product **3**.

Yield 80 %; M.p. 230-232°C;^{13}C NMR (DMSO-d_6, δ ppm):176.1 (C1), 175.1 (C10), 166.2 (C17), 162.3 (C8), 136.2 (C6), 130.1 (C4), 128.0 (C3), 126.5 (C2), 115.2 (C14), 80.4 (C7), 60.2 (C21), 49.3 (C16), 13.8 (C20); ^{1}HNMR (DMSO-d_6, δ ppm):1.22 (t, J = 7.2, 3H, CH_2CH_3),3.18(s, 2H, CH_2),4.16 (q, J = 7.2, 2H, CH_2CH_3), 7.32-8.26 (m, 3H, Ar-H), 7.68 (s, 1H, NH, exchangeable);**IR**(KBr, ν, cm^{-1}): 3241 (NH), 2218 (C≡N),1727, 1665 (2CO);MS; m/z: 321.02(M^{+}); Anal. calcd. for$C_{13}H_{11}N_3O_3S_2$(321.37): C,48.59; H,3.45; N,13.08; Found: C, 48.51; H, 3.39; N, 13.01.

3.2.7. 2-(5-cyano-6-(4,5-dihydrothiophen-2-yl)-4-oxo-1,2,3,4-tetrahydropyrimidin-2-ylthio) acetohydrazide (4)

A mixture of 0.01 mol of compound **3** (3.2 g) and hydrazine hydrate (0.50 g) in ethanol (20 mL) was refluxed for 4h. After cooling the reaction mixture, the product obtained was filtered and dried in air. The solid product was recrystallized from ethanol to obtain the pure product **4**.

Yield 74 %; M.p. 161-163°C; ^{13}CNMR (DMSO-d_6, δ ppm):176.2(C6), 175.3 (C10),169.8(C15), 162.4(C8), 136.2(C1), 130.1(C4), 127.8(C3), 126.5(C2), 115.2(C17), 80.3(C7), 55.6(C14);^{1}HNMR (DMSO-d_6, δ ppm): 2.72 (s, 2H, CH_2), 4.45 (s, H, NH, exchangeable), 7.24-8.22 (m, 3H, Ar-H), 9.96 (s, 1H, NH,exchangeable), 11.20 (s, 1H, NH_2,exchangeable);**IR** (KBr, ν, cm^{-1}): 3446-3190 (NH_2, NH), 2215 (C≡N),1655 (CO);MS; m/z: 307.02(M^{+});Anal. calcd. For $C_{11}H_9N_5O_2S_2$ (307.35): C, 42.99; H, 2.95; N, 22.79; Found: C, 42.91; H, 2.89; N, 22.71.

3.2.8. (Z)-2-(5-cyano-6-(4,5-dihydrothiophen-2-yl)-4-oxo-1,2,3,4-tetrahydropyrimidin-2-ylthio)-N′-(thiophen-2-ylmethylene)acetohydrazide (5)

A mixture of 0.01 mol of compound **4** (3.07 g), thiophene-2-carbaldehyde (1.1 g) and cerium (IV) ammonium nitrate (1.64 g, 0.003 mol) in absolute ethanol (20 mL) was refluxed for 5h. After cooling, the precipitated product was filtered, dried and recrystallized from ethanol to give the pure product **5**.

Yield 75 %; M.p. 133-135°C; ^{13}CNMR (DMSO-d_6, δ ppm):176.3 (C1), 175.4 (C10), 170.7 (C15), 162.3(C8), 144.1(C18), 136.2(C6), 130.2(C4), 129.5(C19), 128.1(C21), 128(C3), 127.1(C20), 126.7(C2), 124.7(C17),115.2(C23), 80.1(C7), 55.8 (C14); ^{1}HNMR (DMSO-d_6, δ ppm): 4.36 (s, 2H, CH_2), 8.40 (s, H, CH=N),7.14-8.22 (m, 6H, Ar-H), 12.23, 12.38 (2s, 2H, 2NH, exchangeable);**IR** (KBr, ν, cm^{-1}): 3438-3213 (NH), 2205 (C≡N)**,** 1651 (CO), **1606** (C=N);MS; m/z: 401.01(M^{+}); Anal. calcd. for$C_{16}H_{11}N_5O_2S_3$(401.48): C, 47.87; H, 2.76; N, 17.44; Found: C, 47.81; H, 2.70; N, 17.38.

CONCLUSION

In this article we reported a novel, green and facile synthesis of substituted pyrimidine derivatives through Biginelli type reaction *via* one-pot reaction of aromatic aldehydes, active methylene compounds and urea or thiourea using choline chloride-urea mixture as a deep eutectic solvent or cerium (IV) ammonium nitrate (CAN) as a catalyst under different conditions. In addition, we synthesized pyrimidnylhydrazide and its corresponding hydrazone.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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