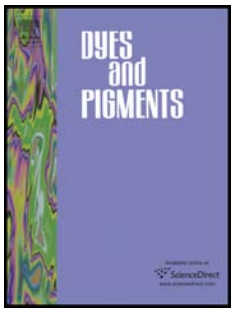
Accepted Manuscript



Greener construction of 4H-chromenes based dyes in deep eutectic solvent

Najmedin Azizi, Mahboobe Mariami, Mahtab Edrisi

PII: S0143-7208(13)00332-X

DOI: 10.1016/j.dyepig.2013.09.007

Reference: DYPI 4081

To appear in: *Dyes and Pigments*

Received Date: 21 July 2013

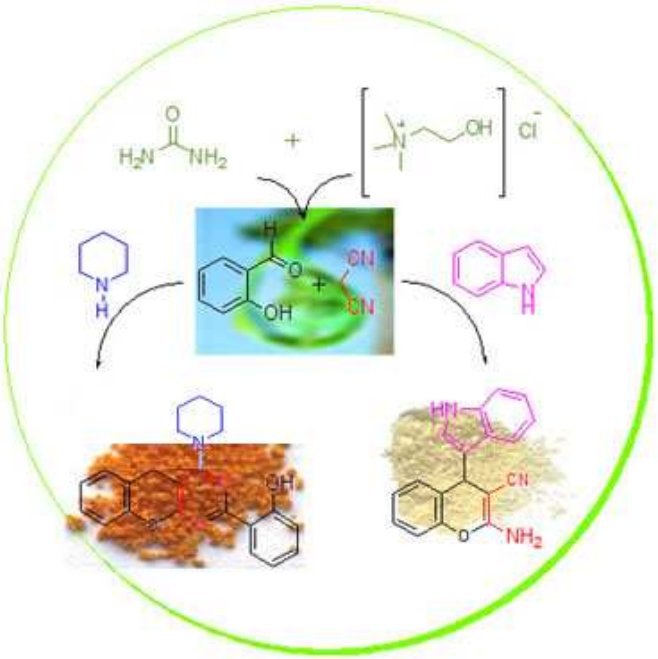
Revised Date: 4 September 2013

Accepted Date: 9 September 2013

Please cite this article as: Azizi N, Mariami M, Edrisi M, Greener construction of 4H-chromenes based dyes in deep eutectic solvent, *Dyes and Pigments* (2013), doi: 10.1016/j.dyepig.2013.09.007.

Greener construction of 4H-chromenes based Dyes in deep eutectic solvent

Najmedin Azizi* Mahboobe Mariami and Mahtab Edrisi



Greener construction of 4H-chromenes based dyes in deep eutectic solvent

Najmedin Azizi* Mahboobe Mariami and Mahtab Edrisi

Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, IranE-mail: azizi@ccerci.ac.ir

Abstract

Green solvents such as deep eutectic solvents are new emerging alternatives to the conventional harmful organic solvents which may find a number of interesting applications in industrial and chemical processes. A facile, atom-economic and environmentally-benign one-pot reaction of salicylaldehyde and malononitrile with various nucleophiles, including indoles, thiols, secondary amines, cyanide and azide were efficiently achieved in choline chloride based deep eutectic solvent (DES).Products distribution of the current green protocol depend on the nature of the nucleophile used in the reaction. The one-pot reaction of salicylaldehyde derivatives and malononitrile with thiols, indoles, and cyanide give 2-amino-3-cyano-4H-chromene derivatives. Secondary amines result in the formation of benzopyrano[2,3-d] pyrimidines, due to the further reaction of salicylaldehyde with 4H-chromene under the same reaction condition. The DES was recycled without any reduction in activity or yield. Therefore, the synthesis of chromene based dyes in green solvents at room temperature under catalyst-free conditions is a promising alternative to previously used procedures.

Keywords: benzopyrano[2,3-d]pyrimidines; choline chloride; 4H-chromene; deep eutectic solvent; salicylaldehyde; malononitrile

1. Introduction

In the context of green chemistry, room-temperature ionic liquids (RTILs) also called molten salts, are green alternatives to the organic solvents, because of their unique properties such as negligible vapor pressure, large liquid range, high thermal stability, more solvation capacity and non-flammability. Cheap and green alternatives to RTILs are DESs. DESs are obtained by complexion of quaternary ammonium salts with hydrogen bond donors such as urea, carboxylic acid, and amide. DESs have many characteristics of conventional ILs (e.g. high thermal stability, the excellent solubility of organic and inorganic substances, low toxicity and nonvolatility) which offer certain advantages. For instance, the preparation of DES in a pure state is easy and economically viable as it shows 100% atom economy with no need to post-synthesis purification that were used for the ILs. Furthermore, choline chloride (ChCl) and urea are both naturally occurring biocompatible compounds that are not hazardous if they release back into the nature. Besides, they are cheap and the processes which use these DESs are economically viable and green [1-10].

Over the past decades, multi-component reactions (MCRs) strives to construct complex molecules in the most efficient possible manner, are becoming one of the major searching

challenges for step-economic syntheses. They are faster and cheaper than classical reactions, since the reaction will be completed by just mixing compounds together in one vessel without isolating any intermediate. The additional benefits to this process are the readily available starting materials, operationally simple, easily automatable, resource effective, atom economy and ecologically benign, with minimization of reaction time, labor, cost, and waste productions [11-14]. Furthermore, MCR with environmentally benign solvents like DES is one of the most suitable strategies for green chemical process and developing the libraries of medicinal scaffolds.

4H-chromene and their derivatives are potentially important structural units in heterocyclic chemistry that exhibits diverse ubiquitous pharmacological properties such as antiviral and anti-nociceptive activities [15-18]. Additionally, due to their spectroscopic properties [19] they are used as fluorescent compounds in laser technology and monitoring of biomolecules. Thus, the synthesis of highly substituted 4H-chromenes and their derivatives has attracted great attention because of their wide applications. Recently, a variety of methods have been reported employing three-component reaction using acidic catalyst or promoter constitutes in the literature [20-34]. However, to the best of our knowledge, there has been only one report about the synthesis of 4H-chromene derivatives in imidazolium-based ionic liquids under catalyst- free condition [17]. Therefore, development of simple and efficient procedures for the catalyst-free synthesis of 4H-chromenes in the novel reaction media is a challenging task. Herein we report an efficient three-component synthesis of 4H-chromenes from salicyldehyde, malononitrile, and different nucleophiles in choline chloride based DESs.

2. Material and methods

2.1 Materials and equipment's:

All starting materials, reagents and solvents are commercially available and were purchased and used without further purification. All products were confirmed by melting point, FTIR spectroscopy, ^{1}HNMR, spectroscopy and mass spectrometry.^{1}H NMR spectra were recorded on 500 MHz NMR and 80 MHz spectrometer in dimethyl sulfoxide (DMSO-d6) and chloroform ($CDCl_3$) using a Bruker Avance 500 or Bruker AC-80 NMR spectrometer. All amines, aldehydes, isocyanides and acids are commercially available. Water and ethanol were distilled before used. All the reactions are monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel with UV light as detecting agents. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. FT-IR spectra were determined on a Bruker Vector-22 infrared spectrometer using KBr disks. Reactions were carried out in 5 mL test tube sealed with a septum. Flash column chromatography was performed with silica gel eluting with ethyl acetate-petroleum ether. Element analyses were carried out on an Elemental Analyzer vario EL cube.

2.2. Deep eutectic solvent preparation

Choline chloride-urea deep eutectic solvent was prepared according to the literature. [1] For DES preparation, urea (200 mmol) and choline chloride (100 mmol) were mixed, stirred and heated until a clear liquid was appeared. The obtained deep eutectic solvent was used without any further purification (Fig. 1).

Fig. 1.

2.3. General procedure for the preparation of 4H-chromene derivatives

Salicylaldehyde (0.5 mmol), malononitrile (0.5 mmol), nucleophile (0.5 mmol), and DES (0.5 mL) were taken in a test tube. The reaction mixture was stirred at room temperature for 15-80 min. After completion of the reaction as indicated by TLC, (in the most cases, reaction mixture were directionally solidified) water (5 mL) was added while stirring and the residue collected by filtration. The resulting solids or viscous liquids were washed with water and was purified by column chromatography or recrystallization with ethanol or diethyl ether to give pure products. For the viscous liquids, ethyl acetate was used for extraction of products. The DES was recovered from the filtrate by evaporating the water phase at 80 °C under vacuum.

2.4. General procedure for the preparation of 4H-chromene [2,3-d]pyrimidine derivatives

Salicylaldehyde (1.0mmol), malononitrile (0.5 mmol), amine (0.60 mmol) were dissolved in choline chloride –urea based deep eutectic solvent (0.5 mL), and were mixed and vigorously stirred at room temperature or 60 °C for 60-200 minutes. After completion of reaction, water was added. The DES being soluble in water and comes in the water layer. The resulting solids were purified by column chromatography or recrystallization with ethanol or ethyl acetate to give pure products. All the products are known and were fully characterized by a comparison with authentic samples.

Selected data

Table 1, entry 1: ^{1}H NMR (DMSO-d_6); $\delta = 5.29$ (s, 1H), 6.65 (d, 1H, J = 7.2 Hz), 7.00 (brs, 2H), 7.10-7.35 (m, 8H); ^{13}C NMR (DMSO-d_6) δ =47.3, 53.2, 114.8, 119.1, 121.3, 124.8, 128.3, 129.2, 130.2, 135.8, 148.1, 160; IR (KBr): 3420, 3310, 2234 cm $^{-1}$ **Table 1, entry 2:** ^{1}H NMR (DMSO-d_6); δ = 2.35 (s, 3H), 5.38 (s, 1H), 6.66-7.45 (m, 10 H); ^{13}C NMR (DMSO-d_6) δ = 25.5,

46.4, 53.1, 114.1, 119.5, 120.9, 124.1, 128.1, 128.4, 128.9, 129.1, 131.0, 136.1, 149.3, 161.2, **Table 1, entry 3:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.35 (s, 1H), 6.64 (d, 1H, J = 7.2 Hz), 7.06-7.12 (m, 6H), 7.21-7.23 (m, 1H), 7.38-7.39 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 46.5, 54.6, 115.1, 118.1, 119.9, 124.6, 126.1, 128.9, 133.1, 134.2, 138.6, 139.8, 146.6, 160.4; **Table 1, entry 4**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.38 (s, 1H), 6.62 (d, 1H, J = 7.8 Hz), 7.01-7.04 (m, 7H), 7.25-7.36 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 46.1, 53.2, 114.8, 119.2, 119.9, 124.1, 125.8, 128.1, 133.9, 134.8, 138.1, 140.4, 147.1, 161.3; **Table 1, entry 5**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.67 (s, 3H), 5.35 (s, 1H), 6.62-7.08 (m, 8H), 7.21-7.39 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.4, 53.1, 54.7, 115.1, 118.1, 118.9, 125.1, 125.9, 128.1, 133.1, 134.5, 137.9, 140.7, 147.7, 160.6; **Table 1, entry 6:** ^{1}H NMR (80 MHz, DMSO-d_6): 5.56 (s, 1 H), 7.44-8.12 (m, 13H): **Table 1, entry 7:** ^{1}H NMR (80 MHz, DMSO-d_6): 2.35 (s, 3H), 5.48 (s, 1 H), 7.01-7.88 (m, 10 H): **Table 1, entry 10**: ^{1}H NMR (500 MHz, DMSO-d_6): 5.42 (s, 1H), 6.62 (d, 1H, J = 7.2 Hz), 7.06-7.42 (m, 8H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 45.9, 53.8, 116.2, 118.1, 119.1, 124.8, 128.1, 129.9, 132.1, 132.9, 136.8, 139.1, 147.9, 160.9; **Table 1, entry 11**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.24 (s, 3H), 5.38 (s, 1H), 6.68-7.42 (m, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.2, 46.4, 54.6, 115.6, 119.1, 119.9, 123.7, 129.6, 130.2, 131.9, 132.5 137.1, 138.6, 148.5, 161.0; **Table 1, entry 12**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.38 (s, 1H), 6.92-7.98 (m, 8H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.1, 54.7, 116.1, 117.2, 119.1, 122.9, 129.1, 130.5, 132.9, 132.5 137.9, 138.9, 146.9, 160.8; **Table 1, entry 13**: ^{1}H NMR (80 MHz, DMSO-d_6): δ = 5.45 (s, 1H), 7.02-8.12 (m, 9H); **Table 1, entry 14**: ^{1}H NMR (80 MHz, DMSO-d_6): δ = 3.68 (s, 3H), 5.42 (s, 1H), 6.54-7.75 (m, 9H); **Table 1, entry 15**: ^{1}H NMR

(80 MHz, DMSO-d_6): δ = 2.35 (s, 3H), 3.68 (s, 3H), 5.52 (s, 1H), 6.54-8.00 (m, 8H); **Table 1, entry 16**: ^{1}H NMR (80 MHz, DMSO-d_6): δ = 5.57 (s, 1H), 3.66 (s, 3H), 6.40-7.90 (m, 8H); **Table 2, entry 1:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.36 (s, 1H), 7.12 (d, 1H, *J*= 8.4 Hz), 7.28 (t, 1H, *J* =7.5 Hz), 7.42-7.46 (m, 2H), 7.52 (brs, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.1, 46.9, 116.1, 117.8, 119.9, 121.6, 125.1, 130.3, 131.2, 148.9, 161.2. IR (KBr): 3388, 3322, 2195, 1658 cm $^{-1}$; **Table 2, entry 3:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.02 (s, 1H), 6.82-7.20 (m, 11H), 10.75 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.4, 56.2, 112.1, 116.9, 119.5, 119.9, 120.1, 120.8, 121.9, 123.8, 124.1, 124.8, 125.4, 127.9, 130.1, 137.6, 148.6, 160.8; **Table 2, entry 4:** ^{1}H NMR (500 MHz, DMSO-d_6): δ =4.68 (d, 1H, *J* = 3.8 Hz), 5.10 (d, 1H, *J* = 3.8 Hz), 7.14 (d, 1H, *J* = 8.0 Hz), 7.27 (dd, 1H, *J* = 7.2 Hz, 1.4 Hz,), 7.39-7.41 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.4, 38.2, 50.1, 112,3, 113.8, 116.8, 120.1, 125.9, 129.4, 131.2, 148.9, 162.8; **Table 2, entry 5:** ^{1}H NMR (80 MHz, DMSO-d_6): δ = 5.49 (s, 1H), 7.28-7.80 (m, 5H); **Table 2, entry 8:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.88 (d, 1H, *J* = 3.7 Hz), 5.26 (d, 1H, *J* = 3.8 Hz), 7.20 (d, *J* = 8.1 Hz, 1H), 7.45-7.72 (m, 4H), ^{13}C NMR (125 MHz, DMSO-d_6) δ = 33.1, 37.8, 49.2, 113.1, 113.8, 116.7, 119.4, 119.9, 121.0, 132.1, 132.7, 149.3, 162.8; **Table 2, entry 9:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 5.34 (s, 1H), 6.79 (m, 5H); **Table 2, entry 11:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.68 (s, 3H), 4.54 (d, 1H, *J* = 3.7 Hz), 5.12 (d, 1H, *J* = 3.8 Hz), 6.98 (dd, 1H, *J* = 7.2 Hz, 1.2 Hz), 7.18 (dd, 1H, *J* = 7.1 Hz, 1.2 Hz), 7.20-7.52 (m 3H). **Table 3, entry 1:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.54-1.60 (m, 6H), 3.42-3.48 (m, 4H), 4.01 (s, 2H), 6.84–7.40 (m, 7H), 8.30 (d, 1H, *J* = 5.8.0 Hz), 12.85 (brs, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.1, 25.8, 26.9, 50.2, 98.4, 115.9, 118.6, 118.9, 119.8, 121.2,

126.1, 128.4, 129.8, 130.2, 134.1, 151.2, 160.8, 161.4, 164.2, **Table 3, entry 2:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.42 (s, 4H), 3.74 (s, 4H), 3.86 (s, 2H), 6.80−8.18 (m, 8H), 11.85 (brs, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.8, 49.2, 67.1, 98.4, 117.1, 118.2, 118.9, 119.8, 120.6, 125.4, 129.1, 129.8, 130.1, 134.1, 150.6, 161.0, 161.5, 163.7, 164.9. **Table 3, entry 3:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.20 (s, 6H), 4.08 (s, 2H), 7.03-7.38 (m, 7H), 8.44-8.46 (m, 1H), 13.25 (brs, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.3, 41.5, 95.2, 117.8, 118.4, 119.8, 120.1, 120.8, 124.8, 128.7, 128.9, 129.9, 134.1, 151.2, 160.9, 161.9, 164.2; **Table 3, entry 5:** ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.64-1.66 (m, 6H, 3.40-3.41 (m, 4H), 3.86 (s, 2H), 6.80−7.62 (m, 5H), 8.18-8.20

(m, 1H), 13.40 (1H, brs, OH)

3. Results and discussion

As a consequence of our interest in the organic synthesis in green solvent as an environmentally attractive media [35-38] and our continual work on the synthesis of heterocyclic chemistry guided by the observation that the presence of salicylaldehyde as simple starting material in biologically heterocyclic moieties. Herein, we describe a mild convenient and simple procedure for the direct synthesis of 4H-chromenes derivatives with one-pot reaction of salicyldehyde **(1)**, malononitrile (**3)**, different nucleophiles (thiols, amines, nitrile, and indoles) without using any catalyst at room temperature with good yields. The experimental procedure is very simple and easy. The biodegradable DES was prepared with simple mixing of choline chloride (100 mmol) and urea (200 mmol) and heated to 80°C in air with stirring till a clear solution was obtained, which was used without any purification. Since this method forms eutectic mixture with no

byproduct formation, it provides 100% atom economy. After preparation of DES, it was found that upon simple mixing of salicyldehyde, (0.5 mmol), thiophenol**,** (0.5 mmol), and malononitrile (0.5 mmol), in choline chloride-urea based DES (0.5 mL), the corresponding product **4** was formed as the only detectable product and isolated in 97 % yield after washing with water and ethanol (Scheme 1). The DES was recovered easily from filtrate by evaporating the water under vacuum and reused for three successions of the reaction without much loss of product yields. Furthermore, it was possible to monitor the reaction visually. A white suspension solution was obtained after addition of the all components to the DES, and the reaction mixture became orange viscose liquid or solids after the reaction is complete. However, the same reaction without DES under solvent-free condition gave only starting materials after 60 minutes.

Scheme 1

On the basis of the interesting results, and in order to establish the generality and scope of these catalyst-free multicomponent reactions, additional reactions of various substituted salicyldehydes with thiols, and malononitrile were carried out under above condition. The results are summarized in Table 1. Not only electron-rich salicyldehyde such as 3-methoxysalicyldehyde but also electron deficient salicyldehyde, 5-bromosalicyldehyde, in the reactions afforded 4H-chromene derivatives in 65–98% yields. Aromatic thiols such as 2-naphthyl thiol and a variety of substituted thiophenols (thiophenol, 4-chloro-thiophenol, 4-bromo-thiophenol, 4-methylthiophene, 4-methoxylthiophenol, 2-methylthiophene) furnished excellent yield of chromene under mild reaction conditions. Electron withdrawing as well as electron-donating substituent on the thiophenol did not make any difference to the reactivity and selectivity of the reaction. Similarly, the corresponding products from the reaction of aliphatic thiols were

obtained albeit in moderate yield and selectivity. The generality of this green protocol was further demonstrated in the reaction between salicyldehydes, and malononitrile with other nucleophiles (**5)** such as cyanide, indoles and secondary aliphatic amines under similar reaction condition. The reaction of salicyldehyde, 5-bromosalicyldehyde and 3-methoxysalicyldehyde, with malononitrile and trimethylsilyl cyanide were performed and the desired products were obtained in short reaction time in 95%, 95% and 92% yields, respectively (Table 2). The reaction of salicyldehyde derivatives with malononitrile and sodium cyanide, indole and malononitrile was also performed under similar reaction conditions and the desired products were isolated in lower yield.

To further highlight the potential of this green methodology a three-component coupling of salicyldehyde , malononitrile , and secondary amines under same reaction condition was developed to provide rapid access to benzopyrano[2,3-d]pyrimidine (Table 3). Furthermore, secondary aliphatic amines such as piperidine, morpholine and dimethyl amine underwent a three-component reaction and leading to the desired product in good yields. However, the reaction fails with primary amine like benzyl amine under this reaction condition. Investigation of the aldehyde scope demonstrated that, 5-bromosalicyldehyde with electron-withdrawing groups performed in a slightly superior manner, and 3-methoxysalicyldehyde were also compatible with the reaction. The reaction setup is quite simple and practical, as it requires only stirring the three components in DES at room temperature. The component of DES is

biodegradable and can be easily accessed from commercially available materials. Moreover, it can easily be prepared and recovered with high efficiency after the reaction.

In order to test the robustness of the procedure that would be an interesting application in industrial and chemical process, a relatively large-scale reaction of salicylaldehyde (10.0 mmol), malononitrile (10.0 mmol), thiophenol (10.0 mmol) in DES (2 mL) in 15 minutes under the optimal conditions were performed. In gram scale, the corresponding product **4** was isolated in 90% yields with simple and clean purification (filtration followed by washing) without any organic solvent (Fig. 2).

Fig. 2

Based On the above observations and the literature survey, the plausible mechanism for the green one-pot reaction in DES is illustrated in Fig.3. The urea components of DES facilitate the Knoevenagel -type condensation through hydrogen bonding between urea and the oxygen of carbonyl groups of salicyldehyde. On the other hand, urea can activate malononitrile so that deprotonation of the C−H bond occurs in the presence of Lewis basic sites of urea and form intermediate (I). Then the higher reactivity of the of salicyldehyde and malononitrile is utilized to facilitate the Knoevenagel condensation to produce intermediate (II), and subsequently

nucleophilic attack of thiophenol to the electron-poor C=C double bond (III) affords 2-amino-2-chromene derivatives 4a (Fig. 3)

Fig. 3

Finally, the recycling of DES was examined using the three component reaction of salicyldehyde, thiophenol and malononitrile in DES (0.5 mL), under optimized conditions. The recovered DES was then reused for three runs without obvious loss of activity (95%, 95%, 90% yields respectively). After completion, water (3 mL) was added to the reaction mixture, shacked vigorously and solid or viscous liquid was separated by filtration. The deep eutectic solvent was recovered from filtrate by evaporating the water phase at 80 ˚C under vacuum and reused for the next batch and recycled again.

4. Conclusion

In summary, we have demonstrated a green, general; three component reaction can take place between salicylaldehyde, malononitrile and different nucleophiles in DES. The novelty of this work is the catalyst free synthesis of chromene and benzopyrano(2,3-d)pyrimidines, using non-toxic, low cost and environmentally benign solvents. This procedure offers additional advantages such as simple workup, general applicability, high isolated product yields which makes it highly suitable for industrial synthesis of biologically active chromene derivatives. Furthermore, it is easy to separate the solvent and product after completion of the reaction with simple workup.

References

[1] Abbott AP, Capper G, Davies DL, Rasheed RK, Tambyrajah V. Novel solvent properties of choline chloride/urea mixtures. Chem Commun 2003;70-71.

[2] Chen Z, Zhou B, Cai H, Zhu W, Zou X. Simple and efficient methods for selective preparation of α-mono or α,α-dichloro ketones and β-ketoesters by using DCDMH. Green Chem 2009;11:275-278.

[3] Gu Y, Jérôme F. Glycerol as a sustainable solvent for green chemistry. Green Chem 2010;12:1127-1138.

[4] Yingying Z, Xiaohua L, Xin F, Yijun S, Xiaoyan J. Properties and Applications of Choline-Based Deep Eutectic Solvents. Prog Chem 2013;25:881-892.

[5] Mamajanov I, Engelhart AE, Bean HD, Hud NV. DNA and RNA in Anhydrous Media: Duplex, Triplex, and G-Quadruplex Secondary Structures in a Deep Eutectic Solvent. Angew Chem Int Ed 2010;49:6310-6314.

[6] Tang S, Baker GA, Zhao H. Ether- and alcohol-functionalized task-specific ionic liquids: attractive properties and applications. Chem Soc Rev 2012;41:4030-4066.

[7] Durand E, Lecomte J, Villeneuve P. Deep eutectic solvents: Synthesis, application, and focus on lipase-catalyzed reactions. Eur J Lipid Sci Technol 2013;115:379–385.

[8] Singh BS, Lobo HR, Pinjari DV, Jarag KJ, Pandit AB, Shankarling GS. Ultrasound and deep eutectic solvent (DES): A novel blend of techniques for rapid and energy efficient synthesis of oxazoles. Ultrason Sonochem 2013;20:287-293.

[9] Phadtare SB, Jarag KJ, Shankarling GS. Greener protocol for one pot synthesis of coumarinstyryl dyes. Dyes Pigm 2013;97:105-112.

[10] Pawar PM, Jarag KJ, Shankarling GS. Environmentally benign and energy efficient methodology for condensation: an interesting facet to the classical Perkin reaction. Green Chem 2011;13:2130-2134.

[11] Gu Y. Multicomponent reactions in unconventional solvents: state of the art. Green Chem 2012;14:2091-2128.

[12] Li M, Zhang B, Gu Y. Facile construction of densely functionalized 4H-chromenes via three-component reactions catalyzed by L-proline. Green Chem 2012;14:2421-2428.

[13] Dömling A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem Rev 2006;106:17-89.

[14] Huang Y, Dömling A. The Gewald multicomponent reaction. Mol Divers 2011;15:3-33.

[15] Kumar D, Reddy VB, Sharad S, Dube U, Suman KA. A facile one-pot green synthesis and antibacterial activity of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes. Eur J Med Chem 2009; 44:3805–3809.

[16] Evdokimov MN, Kireev SA, Yakovenko AA, AntipinMyu, Magedov IV, Kornienko A. Convenient one-step synthesis of a medicinally relevant benzopyranopyridine system. Tetrahedron Lett 2006;47:9309–9312.

[17] Gupta AK, Kumari K, Singh N, Raghuvanshi DS, Singh KN. An eco-safe approach to benzopyranopyrimidines and 4H-chromenes in ionic liquid at room temperature. Tetrahedron Lett 2012;53:650–653.

[18] Evdokimov NM, Kireev AS, Yakovenko AA, Antipin MYu, Magedov IV, Kornienko A. One-Step Synthesis of Heterocyclic Privileged Medicinal Scaffolds by a Multicomponent Reaction of Malononitrile with Aldehydes and Thiols. J Org Chem 2007;72:3443–3453.

[19] Sridevi C, Shanthi G, Velraj G. Structural, vibrational, electronic, NMR and reactivity analyses of 2-amino-4H-chromene-3-carbonitrile (ACC) by ab initio HF and DFT calculations. Spectro chimica Acta, Part A: Molecular and Biomolecular Spectroscopy 2012;89:46–54.

[20] Feducovich SK, Elinson MN, Dorofeev AS, Gorbunov SV, Nasybullin RF, Stepanov NO, Nikishin GI. Electrocatalytic chain transformation of salicylaldehyde and CH acids into substituted 4H_chromenes. Russian Chemical Bulletin, International Edition 2008;57:595-600.

[21] Moafi L, Ahadi S, Bazgir A. New HA 14-1 analogues: synthesis of 2-amino-4-cyano-4H-chromenes. Tetrahedron Lett 2010;51:6270–6274.

[22] Costa M, Areias F, Abrunhosa L, Venancio A, Proencüa F. The Condensation of Salicylaldehydes and Malononitrile Revisited: Synthesis of New Dimeric Chromene Derivatives. J Org Chem 2008;73:1954-1962.

[23] Xie JW, Huang X, Fan LP, Xu DC, Li XS, Su H, Wen YH. Efficient Method for the Synthesis of Optically Active 2-Amino-2-chromene Derivatives via One-Pot Tandem Reactions. Adv Synth Catal 2009;351:3077–3082.

[24] Sugahara K, Kimura T, Kamata K, Yamaguchi K, Mizuno N. A highly negatively charged γ-Keggin germanedeca tungstate efficient for Knoevenagel condensation. Chem Commun 2012;48:8422–8424.

[25] Ren Q, Siau WY, Wang J, Du Z, Zhang K. Expeditious Assembly of a 2-Amino-4H-chromene Skeleton by Using an Enantioselective Mannich Intramolecular Ring Cyclization–Tautomerization Cascade Sequence. Chem Eur J 2011;17:7781–7785.

[26] Yang G, Luo C, Mu X, Wang T, Liu XY. Highly efficient enantioselective three-component synthesis of 2-amino-4H-chromenes catalysed by chiral tertiary amine-thioureas. Chem Comm 2012;48:5880–5882.

[27] Bhat SI, Choudhury AR, Trivedi DR. Condensation of malononitrile with salicylaldehydes and o-aminobenzaldehydes revisited: Solvent and catalyst free synthesis of 4H chromenes and quinolones. RSC Adv 2012;2:10556-10563.

[28] Shanthi G, Perumal PT. An eco-friendly synthesis of 2-aminochromenes and indolyl chromenes catalyzed by $InCl_3$ in aqueous media. Tetrahedron Lett 2207; 48:6785–6789.

[29] Chen W, Cai Y, Fu X, Liu X, Lin L, Feng X. Enantioselective One-Pot Synthesis of 2-Amino-4-(indol-3-yl)-4H-Chromenes. Org Lett 2011;13:4910–4913.

[30] Lakshmi NV, Kiruthika SE, Perumal PT. A Rapid and Efficient Access to 4-Substituted 2-Amino-4H-chromenes Catalyzed by InCl3. Synlett 2011;10:1389–1394.

[31] Chen W, Cai Y, Fu X, Liu X, Lin L, Feng X. Enantioselective One-Pot Synthesis of 2-Amino-4-(indol-3-yl)-4H-Chromenes. Org Lett 2011;13:4910-3.

[32] Yang G, Luo C, Mu X, Wang T, Liu XY. Highly efficient enantioselective three-component synthesis of 2-amino-4H-chromenes catalyzed by chiral tertiary amine-thioureas. Chem Commun 2012;48:5880–5882.

[33] Zonouzi A, Hosseinzadeh F, Karimi N, Mirzazadeh R, Ng SW. Novel Approaches for the Synthesis of a Library of Fluorescent Chromenopyrimidine Derivatives. ACS Comb Sci. 2013, 15, 240-246

[34] Ghahremanzadeh R, Amanpour T, Bazgir A, Pseudo four-component synthesis of benzopyranopyrimidines Tetrahedron Lett, 2010; 51:4202 - 420

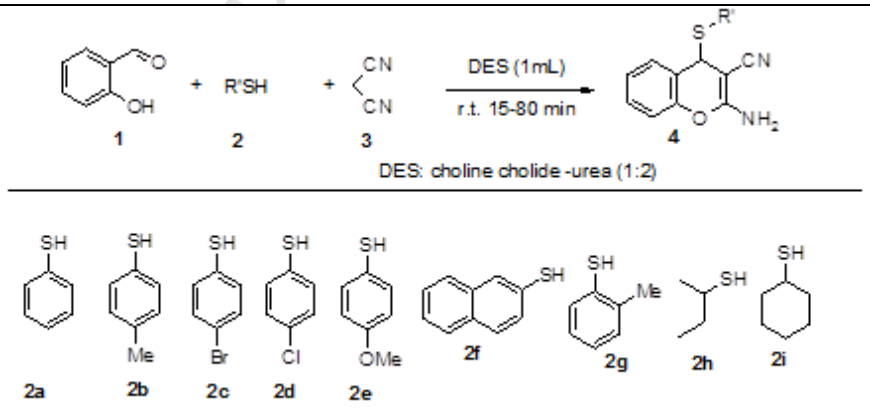
[35] Azizi N, Batebi E. Highly efficient deep eutectic solvent catalyzed ring opening of epoxides. Catal Sci Technol 2012;2:2445-2448.

[36] Azizi N, Gholibeglo E. A highly efficient synthesis of dithiocarbamates in green reaction media. RSC Adv 2012;2:7413-7416.

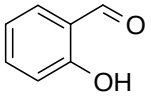
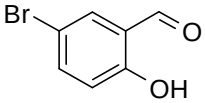
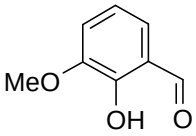
[37] Azizi N, Gholibeglo E, Babapour M, Ghafuri H, Bolourtchian SM; Deep eutectic solvent promoted highly efficient synthesis of N, N'-diarylamidines and formamides. CR Chimie 2012;15:768-773.

[38] Azizi N, Batebi E, Bagherpour S, Ghafuri H. Natural deep eutectic salt promoted regioselective reduction of epoxides and carbonyl compounds. RSC Adv 2012;2:2289-2293.

Table 1 catalyst-free multicomponent synthesis of various substituted 4H-chromene in DES

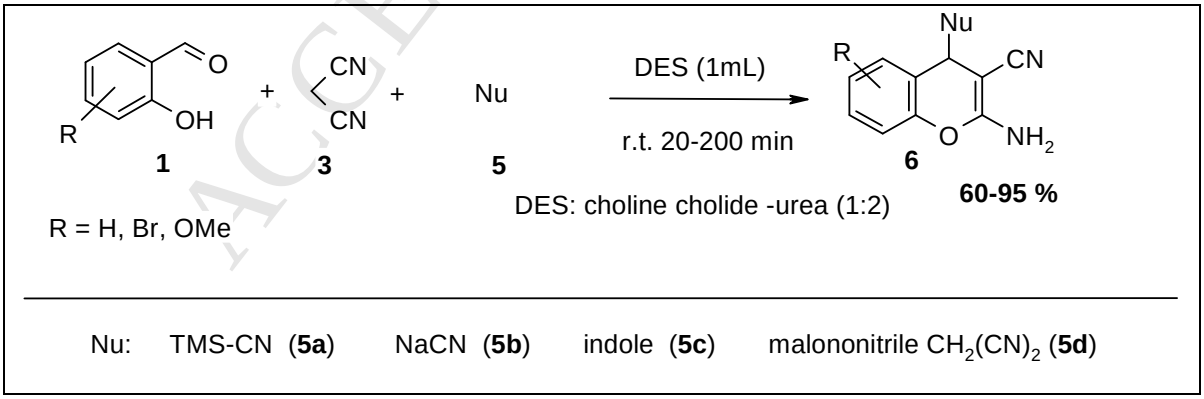


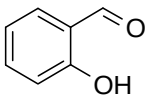
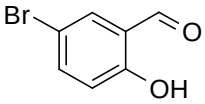
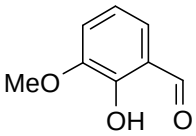
Entry	Salicyldehyde (**1**)	Thiol (**2**)	Yields (%)[a]

1		**2a**	98
2		**2b**	98
3		**2c**	92
4		**2d**	95
5		**2e**	92
6		**2f**	88
7		**2g**	90
8		**2h**	45
9		**2i**	28
10		**2a**	95
11		**2b**	92
12		**2c**	90
13		**2d**	86
14		**2a**	95
15		**2b**	92
16		**2c**	88
17		**2f**	80

[a] Isolated yields

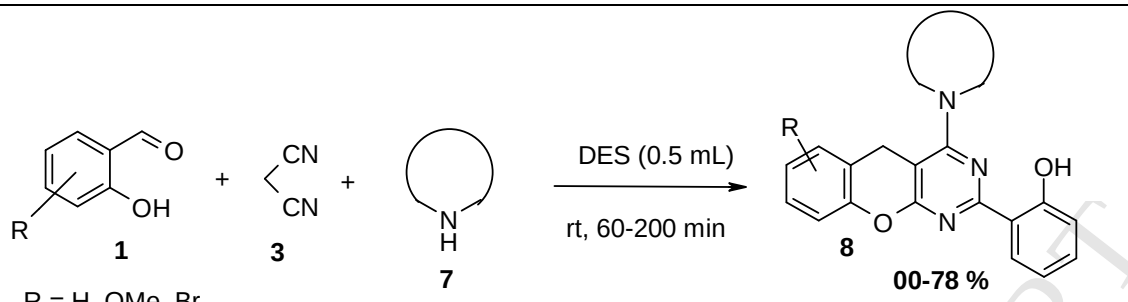
Table 2 DES promoted themulti-component reactions of salicyldehydes and malononitrile with various nucleophiles



Entry	Salicyldehyde (**1**)	Nu (**5**)	Yields (%)[a]
1		**5a**	95
2		**5b**	68
3		**5c**	80
4		**5d**	82
5		**5a**	90
6		**5b**	62
7		**5c**	75
8		**5d**	72
9		**5a**	82
10		**5c**	68
11		**5d**	60

[a] NMR yields

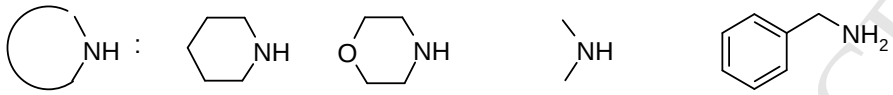
Table 3 Green synthesis of benzopyrano[2,3-d]pyrimidine via a three-component coupling of salicyldehyde, secondary amines, and malononitrile



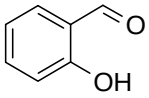
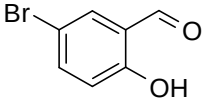
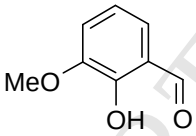
1 **3** **7** **8** **00-78 %**

R = H, OMe, Br

DES: choline cholide -urea (1:2)



7a **7b** **7c** **7d**

Entry	Salicyldehyde (**1**)	amine (**7**)	Yields (%)[a]
1		**7a**	78
2		**7b**	75
3		**7c**	70
4		**7d**	00
5		**7a**	72
6		**7b**	75
7		**7c**	72
8		**7a**	68
9		**7b**	65
10		**7c**	60

[a] NMR yields

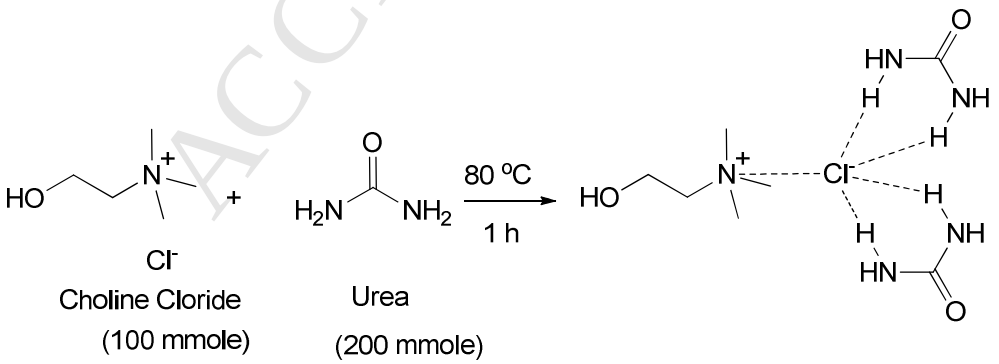


Fig. 1 Deep eutectic solvent preparation

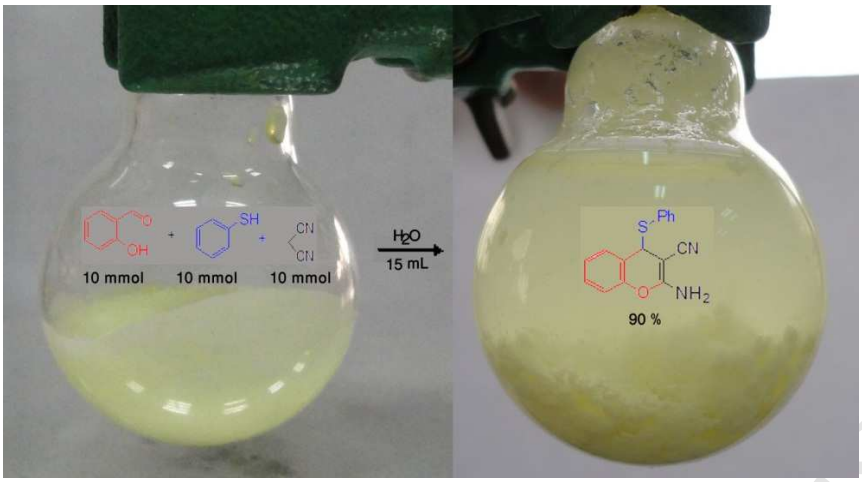


Fig. 2 The gram scale synthesis of 4a in DES

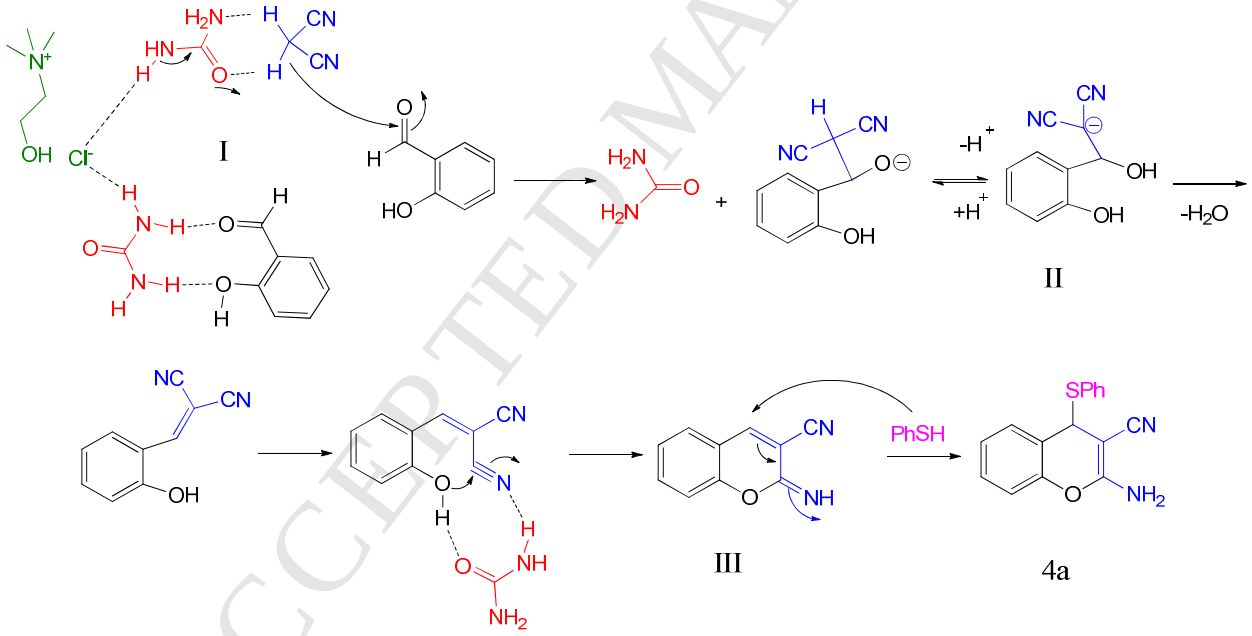
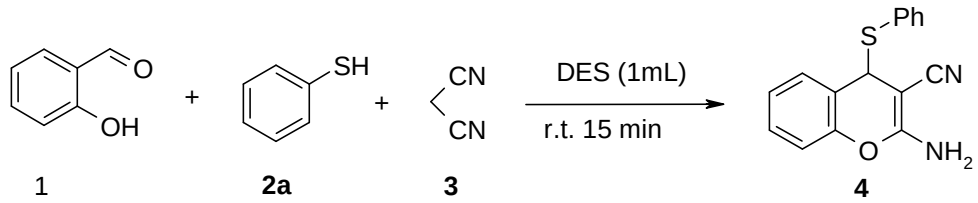


Fig. 3 Plausible mechanistic pathway for the domino synthesis of 4H-chromene derivatives



1 **2a** **3** **4**

Scheme 1. Model reaction in DES (choline chloride-urea)

► Deep eutectic solvents (DES) are green solvents and catalyst for dye synthesis

► Natural products were used as a source for deep eutectic solvents in multicomponent reaction

► This approach eliminates the use of hazardous organic solvents and toxic catalysts.

► Lost cost, wide scope and highly efficient substituted 4H-chromenes were prepared in a single pot using DES