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A facile, choline chloride/urea catalyzed solid phase synthesis of coumarins via Knoevenagel condensation

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Abstract: The influence of choline chloride/urea ionic liquid in solid phase on the Knoevenagel condensation is demonstrated. The active methylene compounds such as meldrum's acid, diethylmalonate, ethyl cyanoacetate, dimethylmalonate, were efficiently condensed with various salicylaldehydes in presence of choline chloride/urea ionic liquid without using any solvents or additional catalyst. The reaction is remarkably facile because of the air and water stability of the catalyst, and needs no special precautions. The reactions were completed within 1hr with excellent yields (95%). The products formed were sufficiently pure, and can be easily recovered. The use of ionic liquid choline chloride/urea in solid phase offered several significant advantages such as low cost, greater selectivity and easy isolation of products.

Keywords: Knoevenagel condensation; coumarins; choline chloride/urea; meldrum's acid; ionic liquid.

1. Introduction

Coumarins are important class of organic compounds having multiple applications in perfume, cosmetic and pharmaceutical industrial production [1]. Many coumarin derivatives are used as photo chemotherapeutic drugs for PUVA (psoralen plus ultraviolet-A-radiation) therapy [2]. Coumarin compounds show a variety of applications i.e., coumarin-1-dye/biphenyl-periodic mesoporous organosilica is used as one of the key ingredient in light harvesting materials [3], furthermore, they are used in the alignment layers of liquid crystal [4], optical brighteners, and dispersed fluorescent and laser dyes [5]. Perkin, Pechmann, Reformatsky,

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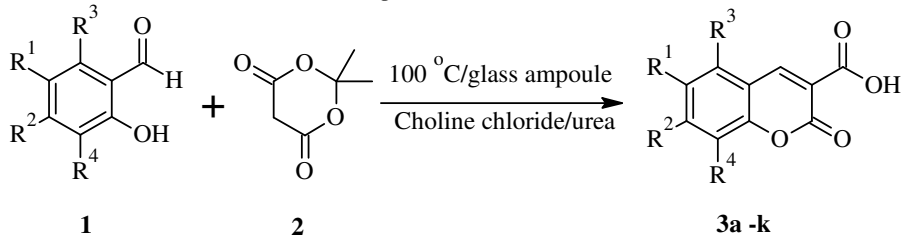
Wittig Knoevenagel reactions [6] are the most common synthetic methods to produce coumarins. The reactions are catalyzed by weak bases or by suitable combinations of amines and carboxylic or Lewis acids under homogeneous conditions [7]. The above well known synthetic routes suffer from the requirement for the use of drastic conditions (acidic or basic), multiple steps, or complicated synthetic operations and lengthy work-up procedures.

The application of environmentally friendly solvents such as ionic liquids is one of the most important areas of green chemistry. The history of ionic liquids started almost hundred years ago with interest in some low temperature melting organic salts as new electrolytes. Recently, room temperature ionic liquids have attracted increasing interest in the area of green chemistry [8-14]. Basic ionic liquids have aroused unprecedented interest because of the advantages such as catalytic efficiency and recycling of the ionic liquid which can be used in the combination of inorganic base and ionic liquid for some base-catalyzed processes [15-16].

In continuation of our work on development of newer methods in various organic synthesis [17-28], in this paper we report a very efficient, fast and general procedure where the condensation of salicylaldehyde, and its derivatives with various active methylene compounds such as meldrum's acid, ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate in the presence of choline chloride/urea ionic liquid under solid phase produced various coumarins (Scheme 1, 2). The method offers several advantages because organic solvents are often expensive, toxic, difficult to remove in case of aprotic dipolar solvents with high boiling point, and are environmentally polluting. Ionic liquid prevents the risk of hazardous explosions when reaction takes place in solid phase system. The reactions (i.e. the synthesis of coumarins) were usually complete within 1-4 hr that gave improved yield (95%) over conventional methods (7-9 hr, 70-80 % Yield). Moreover, the synthesis of choline chloride/urea ionic liquid is fast, easy, cost effective and very simple to workup.

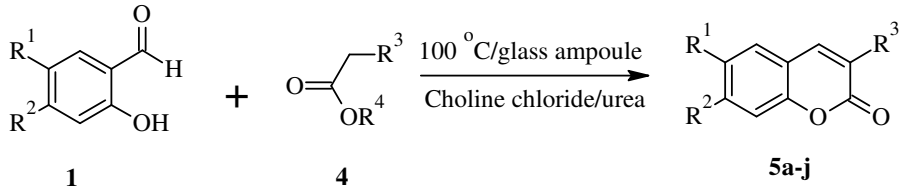
2. Results and discussion

In the initial exploratory experiments, the reaction of salicylaldehyde (2.0 g, 0.0164 mol) and meldrum's acid (2.134 g, 0.0164 mol) was carried out in the presence of ionic liquid choline chloride/urea in solid phase (14.87 g, 5 mole equivalent) to afford the coumarin-3-carboxylic acid. The reaction is remarkably facile, because of the air and water stability of the catalyst. The experiment was carried out to establish the optimal amount of ionic liquid choline chloride/urea in solid phase. The conventional method of preparation was also studied and was found that, ionic liquid choline chloride/urea in solid phase gave better result in 1-4 hr (95% yield) compare to conventional method (7-9 hr, 70-80 % Yield). Apart from high yield, the other advantage in using ionic liquid is its high solubility in water, which makes it perfect in the isolation of the products. Similarly by adopting optimized reaction conditions, various coumarins were prepared with ethyl cyanoacetate, diethylmelonate, dimethyl malonate etc., in presence of 5 mol equivalent of ionic liquid (Scheme 2).The results are reported in Table 2. The conventional method of synthesizing coumarins via Knoevenagel method requires piperidine as base and large amount of ethanol. For example, to synthesize quantity of 1 gram of coumarins through Knoevenagel reaction requires 50 ml ethanol as medium including for washing and recrystallisation of the crude products. Therefore, the synthesis of coumarin derivatives using choline chloride/urea ionic liquids is more convenient than conventional methods.



1 **2** **3a -k**

Scheme 1 Direct synthesis of Coumarin-3-carboxylic acids **3a-k**



1 **4** **5a-j**

Scheme 2 Synthesis of various 3-substituted coumarins via Knoevenagel condensation **5a-j**

Table1. Reaction yield and melting points of newly synthesized compounds **3a-k**.

Entry	R^1	R^2	R^3	R^4	Yield (%)	Mp(obs)/(litr) °C
3a	H	H	H	H	98	191-192/193-194[29]
3b	Cl	H	H	H	97	118-120/120-121[29]
3c	Br	H	H	H	93	195-198/195-196[29]
3d	H	Et_2N	H	H	96	243-248/222-224[29]
3e	H	OH	H	H	97	259-262/261-263[29]
3f	H	Morpholine	H	H	96	243-244
3g	H	$CH(CH_3)_2$	H	H	95	106-109
3h	H	H	H	OCH_3	97	215-216/218[7]
3i	CH_3	H	H	H	95	163-164/166[7]
3j	H	OCH_3	H	H	96	190-195/192-194[29]
3k	H	F	H	H	98	200-203

Table 2. Reaction yield and melting points of newly synthesized compounds **5a-j.**

Entry	R^1	R^2	R^4	R^3	Yield (%)	Mp(obs)/(litr) ^oC
5a	H	H	Et	COOMe	96	121-122/124[30]
5b	H	H	Et	COOEt	95	92-93/93-94[30]
5c	H	H	Et	CN	98	180-182/184-185[30]
5d	H	Et_2N	Et	COOMe	94	149-152/151-153[30]
5e	H	Et_2N	Et	COOEt	98	80-82/77-78[30]
5f	H	Et_2N	Et	CN	98	225-226/229[30]
5g	H	$CH(CH_3)_2$	Et	CN	92	125-127
5h	H	Morpholine	Et	CN	96	262-264
5i	H	OMe	Et	CN	95	221-223/224-226[30]
5j	H	Cl	Et	CN	98	189-192

3. Conclusion

The application of environmentally friendly solvents such as ionic liquids is one of the most important areas of green chemistry. The use of choline chloride/urea catalyzed solid phase synthesis of coumarins via knoevenagel condensation has not only yielded the products in good yield, but was also very effective in terms of time consumption, which makes the ionic liquid mediated synthesis more effective in generating new chemical entities useful in the field of drug discovery and fluorescence studies.

4. Experimental

All the melting points were recorded in open capillaries. The purity of the compounds was monitored by TLC on silica gel and was purified by recrystallization with ethonal.^{1}H NMR spectra were recorded on a Bruker-400MHz spectrometer using TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra was recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

4.1. Preparation of Ionic liquid (ILs)

The ionic liquid choline chloride/urea was prepared according to the procedures reported in literature[31] by heating a mixture of choline chloride and urea with a molar ratio of 1:2 at 80 ^{o}C until a homogeneous liquid was formed.

4.2. General procedure for the synthesis of coumarins:

Synthesis of coumarin-3-carboxylic acid (3a)

The salicylaldehyde (2.0 g, 0.0164 mol) and meldrum's acid (2.36 g, 0.0164 mol) and choline chloride/urea (5 equivalent) taken in a glass ampoule and heated at 100 ^{o}C for 1hr time (Table 13a-k). After the completion of reaction as indicated by TLC, the reaction mixture was poured into ice water (150 cm^3) stirred well and the solid product obtained was filtered and recrystallized by ethanol. Further the filtrate having choline chloride/urea was recovered under reduced pressure and reused in subsequent reactions, showing the same catalytic activity. All other compounds were similarly prepared.

7-(morpholin-4-yl)-2-oxo-2H-chromene-3-carboxylic acid *(3f).* Orange crystalline solid: IR (KBr): ν = 1716 (C=O)cm^{-1}, 1676 (C=O)cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): (δ/ppm): 12.41 (br, 1H), 8.58 (s, 1H), 7.68 (d, , 1H, *J* = 9.0 Hz), 7.03 (dd, 1H, *J* = 2.2, 8.9 Hz), 6.85 (d, 1H, *J* = 2.2 Hz), 3.72-3.75 (m, 4H), 3.42-3.44 (m, 4H). ^{13}C NMR(100 MHz, DMSO-d_6): (δ/ppm): 164.8, 159.0, 157.8, 155.7, 149.6, 131.8, 111.7, 110.5, 109.4, 98.9, 66.1, 47.03. MS.*m/z* = 276 (M+1),277(M+2). Anal.Calcd for $C_{14}H_{13}NO_5$: C, 61.09 %; H, 4.76 %; N, 5.09 %. Found:C, 60.96 %; H, 5.04 %, N, 4.85 %.

2-oxo-7-(propan-2-yl)-2H-chromene-3-carboxylic acid *(3g).* White crystalline solid: IR (KBr): ν = 1740 (C=O)cm^{-1}, 1680 (C=O)cm^{-1}: ^{1}H NMR(400 MHz,DMSO-d_6): (δ/ppm): 13.12 (br,s,1H), 8.71 (s,1H), 7.82(d, ,1H, *J* = 8.41 Hz), 7.3-7.33(m, 2H), 3.01-3.04(m,1H), 1.24 (d, 6H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz,DMSO-d_6): (δ/ppm): 164.5, 157.4, 156.6, 155.2, 148.8, 130.5, 123.9, 117.6, 116.4, 114.1, 34.2, 23.7. MS.*m/z* = 233 (M+1). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23 %, H, 5.21 %. Found: C, 67.29%; H, 5.31%.

7-Fluoro-2-oxo-2H-chromene-3-carboxylic acid*(3k).* White crystalline solid: IR (KBr): ν = 1735 (C=O)cm^{-1}, 1693 (C=O)cm^{-1} ^{1}H NMR (400 MHz, DMSO-d_6): (δ/ppm):13.39 (s,1H), 8.7 (s, 1H), 7.79 (dd, 1H, *J* = 2.9, 8.3 Hz), 7.58-7.68 (m, 1H),7.48-7.52 (m,1H).^{13}C NMR (100 MHz,DMSO-d_6): (δ/ppm): 163.7, 159.1, 156.7, 156.3, 150.9, 147.2, 121.6, 121.3, 119.4, 118.9, 118.8, 118.2, 118.1, 115.1, 114.9. MS,*m/z* = 206 (M-2). Anal.Calcd for: $C_{10}H_5FO_4$,C, 57.71 %; H, 2.42 %. Found: C, 57.69 %; H, 2.40 %.

2-oxo-7-(propan-2-yl)-2H-chromene-3-carbonitrile *(5g).*

White crystalline solid: IR (KBr): ν = 1722 (C=O)cm^{-1}, 2232(C≡N), ^{1}H NMR(300 MHz,DMSO-d_6): (δ/ppm,): 8.91 (s, 1H), 7.73 (d, 1H, *J* = 7.9 Hz), 7.40 (t, 2H *J* = 8.8 Hz), 3.02-3.09 (m, 1H), 1.25 (d, 6H, *J* = 6.86 Hz). ^{13}C NMR (100 MHz,DMSO-d_6): (δ/ppm): 158.0, 157.6, 154.8, 153.7, 130.3, 124.5, 116.0, 115.2, 114.8, 101.3, 34.3, 23.6. MS.*m/z* = 214 (M+1). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23 %; H, 5.20 %; N, 6.57 %. Found: C, 73.22 %; H, 5.35 %; N, 5.61 %.

7-(morpholin-4-yl)-2-oxo-2H-chromene-3-carbonitrile *(5h).* White crystalline solid: IR (KBr): ν = 1731 (C=O)cm^{-1},2203(C≡N), ^{1}H NMR(400 MHz, DMSO-d_6): (δ/ppm): 8.64 (s, 1H), 7.57 (d, 1H, *J* = 9.0 Hz), 7.04-7.09 (m, 2H),6.9(d,1H, *J* =2.2) 3.73(q.4H, *J* = 5.0Hz,14.0Hz),3.47(t,4H, *J* = 4.6Hz) ^{13}C NMR (100 MHz,DMSO-d_6): (δ/ppm): 165.8, 157.8, 157.0, 153.6, 131.7, 115.4, 114.3, 111.7, 101.4, 97.9, 57.17, 23.5, 19.6, 13.9.MS.*m/z* = 257 (M+1). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62 %; H, 4.72 %; N, 10.93 %. Found: C, 65.51 %; H, 4.69 %; N, 10.89 %;

7-chloro-2-oxo-2H-chromene-3-*carbonitrile (5j).* White crystalline solid: IR (KBr): ν = 1716 (C=O)cm^{-1}, 1676 (C=O)cm^{-1} ^{1}H NMR(400 MHz,DMSO-d_6): (δ/ppm): 7.55-7.57 (m, 1H), 8.95 (s, 1H), 7.77-7.85 (m, 2H), ^{13}C NMR (100 MHz,DMSO-d_6): (δ/ppm),: 165.7, 157.6, 154.9, 153.0, 131.69, 126.30, 117.50, 111.65, 101.38, 97.83. MS.*m/z* = 208 (M+3). Anal.Calcd for $C_{10}H_4NO_2$: C, 58.42 %; H, 1.96%; N, 6.81%. Found: C, 58.49 %; H, 1.92 %; N, 6.80 %.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/OC

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