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Aqueous synthesis of coumarins using tetramethylammonium hydroxide as surfactants

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ABSTRACT

A simple protocol was established to synthesize various coumarins using Tetramethylammonium hydroxide as a phase transfer catalyst in water. For coumarin synthesis, the active methylene compounds such as diethyl melonate, meleno nitrile, ethyl aceto acetate, was used with salicylaldehyde, and 2-hydroxy-1-naphthaldehyde in the presence of catalytic amount of piperidine in water and Tetramethylammonium hydroxide. This process is a practical synthetic method for the preparation of various 3-substituted coumarins and benzocoumarins. The influence of surfactant in water on the Knoevenagel is demonstrated. The products formed were 100% pure and high yield and coumarin product could simply be separated via filtration.

KEYWORDS

Knoevenagel coumarin synthesis;
Tetramethylammonium hydroxide;
Active methylene compounds;
Piperidine;
One pot.

INTRODUCTION

Coumarin (2*H*-1-benzopyran-2-one) and coumarin derivatives are natural compounds[1] and are important chemicals in the perfume, cosmetic, and pharmaceutical industrial production[2]. Knoevenagel reaction[3], a century old reaction, is one of the most common synthetic methods to produce coumarins. The process consists of condensation of salicylic aldehydes with malonic acid or esters giving the coumarin-3-carboxylic acids or esters that successively undergo decarboxylation. The reaction was catalyzed by weak bases or by suitable combinations of amines and carboxylic[4] or Lewis[5] acids under homogeneous conditions. Surfactants were useful for micellar reactions[6,7], emulsion polymerization[8,9], phase-transfer reactions[10,11], and other organic syntheses.

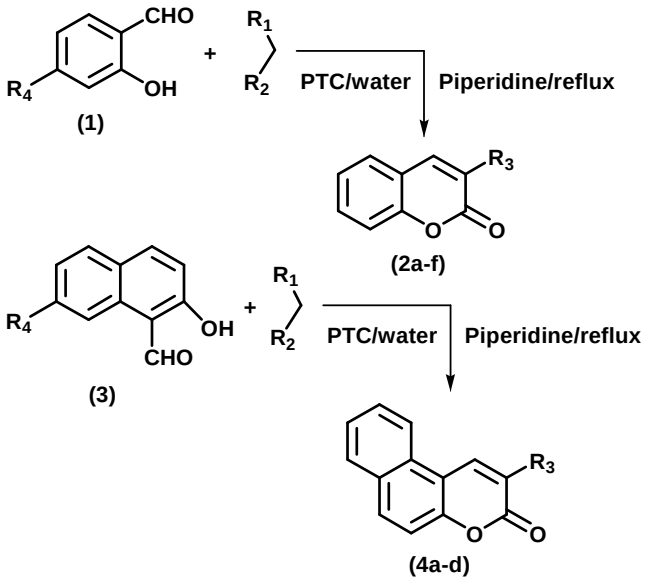
The well known synthetic routes to coumarins including the Perkin, Raschig, Pechmann, Knoevenagel and Wittig reactions suffer from the requirement for the use of drastic conditions (acidic or basic), multiple steps, complicated synthetic operations and lengthy work-up procedures.

The aim of the present paper is to reveal that under surfactant and water system the Knoevenagel condensation could be successfully applied to the synthesis of a number of coumarins and the scope of the method is very broad. We report a very simple, fast and general procedure where the condensation of salicylaldehyde, 2-hydroxy-1-naphthaldehyde or its derivatives with various active methylene compounds (ethyl aceto acetate,

diethyl melonate and meleno nitrile etc) in the presence of catalytic amount of piperidine under surfactant-water system leading to the synthesis of coumarins (Scheme 1). Surfactant-water system offers several advantages: solvents are often expensive, toxic, difficult to remove in case of aprotic dipolar solvents with high boiling point, and are environmentally polluting agents. Water as solvent prevents the risk of hazardous explosions when reaction takes place in surfactant-water system. The reactions (i.e the synthesis of coumarins) were usually complete 15-20 hr that gave improved yield over conventional methods. Moreover, the work-up procedure is simply reduced to the recrystallization of product from solvent if required. Experimental results are given in TABLE 1. The use of tetramethylammonium hydroxide offered several significant advantages such as low cost, greater selectivity, and easy isolation of products. To the best of our knowledge, tetramethylammonium hydroxide in water has not been employed in Knoevenagel method of coumarin synthesis. This work was encouraged by our previous investigation on new routes and new synthesis of various heterocyclic compounds[12-22].

RESULTS AND DISCUSSION

In the initial exploratory experiments, the reaction of salicylaldehyde, 2-hydroxy-1-naphthaldehyde (2.0 g, 0.0164 mol) and ethyl aceto acetate (2.134 g, 0.0164 mol) was carried out in the presence of surfactant Tetramethylammonium hydroxide (0.15g, 10 mol %) and catalylitical amount of piperidine in water to afford the 3-acetyl coumarin. In the experiments carried out to establish the optimal amount of surfactant, the reaction with a 10 mol% surfactant loading gave good yield (TABLE 1). However the same result was observed, when 20 mol% of surfactant was used and the reaction time was also found to be same. Further increasing amount of the surfactant did not change the isolated yield and reaction time. The conventional method of preparation was also studied and it was found that, water gave the same results as ethanol. Apart from high yields the other advantage in the use of surfactant was its high solubility in water which makes the isolation of the product from reaction mixture easy. Similarly by adopting optimized reaction conditions, the various coumarins was prepared with cyano ethyl acetate, meleno nitrile, diethyl melonate etc in presence of 10 mol% surfactant in water (Scheme 1). The results are reported in TABLE 1. The conventional method of synthesizing coumarins via Knoevenagel method require large amount of ethanol. For example, to synthesize 1gm coumarin utilizes 50ml (including as medium, washing and recrystallization). Another important factor in knoevenagel is the reflex temperature was not suitable for preparing coumarins when ethanol was used as solvent. When replacing ethanol with water in the presence of suitable phase transfer catalyst it is possible to get products in good yield at reflex temperature.



Scheme 1

	R_1	R_2	R_3	R_4
2a & 4a	$COCH_3$	COOEt	$COCH_3$	H
2b & 4b	COOEt	COOEt	COOEt	H
2c & 4c	CN	CN	CN	H
2d	COOEt	COOEt	$COOCH_3$	OH
4d	$COOCH_3$	$COOCH_3$	$COOCH_3$	H
2e	$COOCH_3$	$COOCH_3$	$COOCH_3$	OH
2f	CN	CN	CN	OH

EXPERIMENTAL

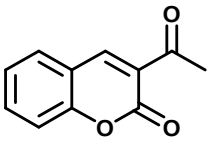
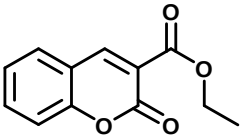
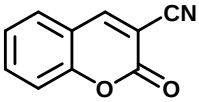
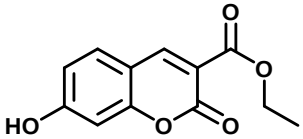
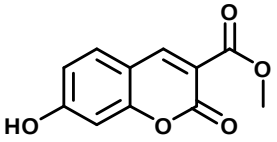
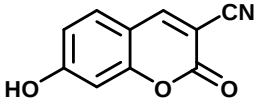
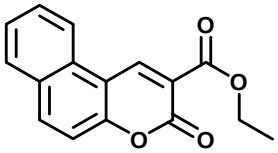
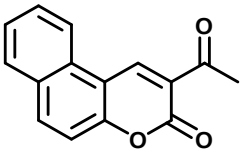
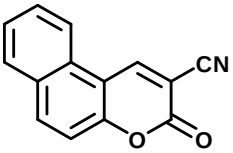
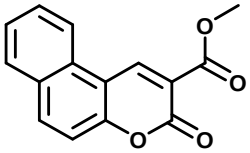
All the melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and was purified by column chromatography. ^{1}H NMR spectra was recorded on a Bruker-400 Hz spectrometer using *TMS* as an internal standard. IR spectra was obtained using a FTS-135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

General procedure for the synthesis of coumarins

Synthesis of 3-Acetyl coumarin (2a)

The salicylaldehyde (2.0 g, 0.0164 mol) and ethyl acetoacetate (2.134 g, 0.0164 mol) and catlytical amount of piperidine was dissolved in 20 ml water. Tetra methyl ammonium hydroxide (0.15g, 10 mol %) was added to the reaction mixture and refluxed on water bath for the appropriate time (TABLE 1). After the completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and poured into water (150 cm^3) and the product obtained was filtered and recrystallised by water. All other compounds were similarly prepared

TABLE 1 : Knoevenagel reaction between salicylaldehyde, 2-hydroxy-1-naphthaldehyde and ethyl aceto acetate, cyano ethyl acetate, diethyl melonate catalysed by 10 mol % tetramethylammonium hydroxide in water.

Entry	Products	Time/ hr	Yield/ (%)	M.p.^{0}C/ M.p.^{0}C Lit
2a		10	83	118-120 (119-122)
2b		9	90	93-95 (92-94)
2c		8	86	192-194 (189-190)
2d		17	87	172-174 (173-175)
2e		14	84	266-268 (265-270)
2f		13	82	252-254 (249-251)
4a		15	85	115-116 (117-118)
4b		18	86	188-190 (186-188)
4c		15	81	290-292 (296-298)
4d		18	79	172-174 (168-170)

3-Acetyl coumarin (2a)

White crystalline solid; IR (KBr): ν = 1758 (C=O) cm^{-1}, 1750 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.7 (s, 3H, CH_3), 7.4 (m, 2H, ArH), 7.8 (m, 2H, ArH), 8.6 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 197.1 (C=O), 163 (C=O), 151, 149, 131.6, 128.5, 127, 126.6, 120, 125.7, 22.8 ppm; MS: m/z = 189 (M+1).

Ethyl coumarin-3-carboxylate (2b)

White crystalline solid; IR (KBr): ν = 1760 (C=O) cm^{-1}, 1745 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 7.4 (m, 2H, ArH), 7.8 (m, 2H, 2H), 8.6 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 166.2 (C=O), 163 (C=O), 153, 151.2, 128.6, 128.3, 127, 125.8, 122.6, 121.8, 60.1, 14.3. ppm; MS: m/z = 219 (M+1).

3-Cyano coumarin (2c)

Yellow crystalline solid; IR (KBr): ν = 1760 (C=O) cm^{-1}, 2258 (CN) cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5 (m, 2H, ArH), 7.8 (m, 2H, ArH), 8.7 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 163 (C=O), 160, 151.2, 128.7, 128.3, 126.5, 125.6, 121.5, 118 (CN), 100.4, ppm; MS: m/z = 172 (M+1).

Ethyl benzocoumarin-3-carboxylate (4a)

Yellow crystalline solid; IR (KBr): ν = 1765 (C=O) cm^{-1}, 1750 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$: δ = 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 7.4 (d, 1H, ArH), 7.5 (t, 1H) 7.7 (t, 1H) 7.9 (d, 1H) 8.1 (d, 1H) 8.3 (d, 1H) 9.3 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 166 (C=O), 163 (C=O), 152.5, 151.2, 132.3, 130, 129.3, 128.6, 127.8, 123.7, 122.8, 122.4, 117.5, 117.3, 60, 14.1. ppm; MS: m/z = 269 (M+1).

3-Acetyl benzocoumarin (4b)

Yellow crystalline solid; IR (KBr): *v* = 1765 (C=O) cm^{-1}, 1746(C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-

d6): δ = 2.7 (s, 3H, CH_3), 7.6 (m, 2H, ArH), 7.8 (d, 1H, ArH), 8.1 (d, 1H, ArH), 8.3 (d, 1H, ArH), 8.6 (d, 1H, ArH), 9.3 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 197.1 (C=O), 163.5 (C=O), 151.2, 150.7, 132.2, 132, 130.2, 129, 128.9, 127, 123.6, 123, 117.7, 117.4, 22. δ ppm; MS: m/z = 239 (M+1).

3-Cyano benzocoumarin (4c)

Yellow crystalline solid; IR (KBr): ν = 1768 (C=O) cm^{-1}, 2256 (CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 7.6 (m, 1H, ArH), 7.9 (d, 1H, ArH), 8.0 (d, 1H, ArH), 8.4 (d, 1H, ArH), 8.7 (d, 2H, ArH), 9.3 (s, 1H, CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 163 (C=O), 160.6, 151.3, 132.2, 130.2, 129.1, 128.6, 127, 123.8, 122.4, 117.6, 117.5, 117.2, 100.3 δ ppm; MS: m/z = 222 (M+1).

CONCLUSION

In summary, the method leads to a notable improvement in reaction conditions for coumarin synthesis by Knoevenagel condensation in water and Tetra methyl ammonium hydroxide (10 mol %) as phase transfer catalyst at reflux temperature.

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REFERENCES

[1] **(a)** F.M.Dean; 'Naturally Occurring Oxygen Ring Compounds', Butterworth, London, 53-81 **(1963)**; **(b)** T.O.Soine; J.Pharm.Sci., **53**, 231 **(1964)**; **(c)** R.D.H.Murray, J.Mendez, S.A.Brown; 'The Natural Coumarins: Occurrence, Chemistry and Biochemistry', Wiley, New York, **(1982)**.

[2] **(a)** W.C.Meuly; 'Kirk-Othmer Encyclopedia of Chemical Technology', 3rd Edition, John Wiley and Sons, New York, **7**, 196-906 **(1979)**; **(b)** D.M.Stuart, J.K.Hruschka; Ibid. **16**, 951-955; **(c)** W.I.Taylor, B.Chant, G.van Loveren; Ibid. **4**, 15.

[3] **(a)** E.Knoevenagel; Chem.Ber., **29**, 172 **(1896)**; **(b)** E.Knoevenagel; Chem.Ber., **31**, 730 **(1898)**; **(c)** G.Jones; 'Organic Reactions', Wiley, New York, **15**, 204 **(1967)**; **(d)** L.F.Tietze, U.Beifuss, B.M.Trost, I.Fleming, C.H.Heathcock, (Eds); 'In Comprehensive Organic Synthesis', Pergamon Press, Oxford, Chapter 1.11, **2**, 341-394 **(1991)**.

[4] M.Baltorowicz; Pr.Inst.Przem.Org., **2**, 33 **(1970)**; Chem.Abstr., **78**, 58190 **(1973)**.

[5] B.Green, R.I.Crane, I.S.Khaidem, R.S.Leighton, S.S.Newaz, T.E.Smyser; J.Org.Chem., **50**, 640 **(1985)**.

[6] J.H.Fendler, E.J.Fendler; 'Catalysis in Micellar and Macromolecular Systems', Academic Press, New York, **(1975)**.

[7] M.Nakamura, N.Tsutsui, T.Takeda, T.Tokoroyama; Tetrahedron.Lett., **25**, 3231 **(1984)**.

[8] C.W.Cart, I.M.Kolthoff, E.J.Meehan, D.E.Williams; J.Polym.Sci., **5**, 201 **(1950)**.

[9] W.P.Weber, G.W.Gokel; 'Phase Transfer Catalysis in Organic Synthesis', Springer-Verlag, Berlin, **(1977)**.

[10] E.V.Dehmlow, S.S.Dehmlow; 'Phase Transfer Catalysis', Verlag Chemic. Weinheim. Deerfield Beach (Florida), Basel, **(1980)**.

[11] A.Lubenau, J.Auge, Y.Queneau; Synthesis, 741 **(1994)**.

[12] A.G.Mahesh, H.Jayadevappa, A.Sudhakara, K.M.Mahadevan; Lett.Org.Chem., **5**, 628 **(2008)**.

[13] A.Srinivasa, K.M.Mahadevan, T.H.S.Kumara, H.Vijaykumar; Monatsh.Chem., **139**, 1475 **(2008)**.

[14] H.N.Harishkumar, H.VijayKumar, K.M.Mahadevan; Synth.Commun., **40**, 1-9 **(2010)**.

[15] V.P.Prabhakara, B.S.Sherigara, K.M.Mahadevan, H.Vijaykumar; Synth.Commun., **40**, 2220 **(2010)**.

[16] A.Sudhakara, H.Jayadevappa, K.M.Mahadevan, H.Vijaykumar; Synth.Commun., **39**, 1-10 **(2009)**.

[17] Rajesha, H.S.B.Naik, H.N.H.Kumar, K.M.Hosamani, K.M.Mahadevan; Arkivoc., **2**, 11-19 **(2009)**.

[18] A.Srinivasa, K.M.Mahadevan, H.Vijaykumar; Synth.Commun., **39**, 93 **(2009)**.

[19] V.P.Prabhakara, B.S.Sherigara, K.M.Mahadevan, H.Vijaykumar; Synth.Commun., **39**, 158 **(2009)**.

[20] A.Srinivasa, V.P.Prabhakar, H.Vijaykumar, K.M.Mahadevan; Monatsh.Chem., **139**, 111 **(2008)**.

[21] A.Srinivasa, K.M.Mahadevan, K.M.Hosamani, H.Vijaykumar; Monatsh.Chem., **139**, 141 **(2008)**.

[22] A.Srinivasa, K.M.Mahadevan, H.Vijaykumar; Monatsh.Chem., **139**, 255 **(2008)**.