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One-Pot Greener Protocol for the Synthesis of Substituted Coumarins

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An expeditious one-pot procedure for the synthesis of substituted coumarins under microwave irradiation is accounted. The method describes an easy and fast method for the synthesis of substituted acetoxy coumarins which are very good fluorophores for medical as well as industrial applications. It makes use of easily available reagents such as triethylamine and acetic anhydride as catalyst. The method finds good applications for the synthesis of multisubstituted coumarins.

Key Words: Coumarins, Acetoxy coumarins, Microwave irradiation, Triethylamine, Acetic anhydride.

INTRODUCTION

Coumarins are valuable species due to their extensive commercial, biological and pharmacological potentials. Coumarin derivatives have found applications as antibiotics[1-3], antimicrobial[4], antioxidant[4,5], antiinflammatory[5], anticancer agents[6] and as HIV proliferators[7]. The odoriferous and fluorescent nature of coumarin derivatives led to their wide spread use in industries as perfumery chemicals, food additives[8], optical brightening agents[9,10] and dispersed fluorescent and laser dyes[11].

Many methods have been developed for the synthesis of these highly active compounds both under conventional and modern methodologies, which include Claisen rearrangement[12], Perkins' reaction[13], Von Pechmann reaction[14], Knoevenagel condensation[15], Wittig reaction[16] *etc*. and the modified version of these methods[17-25]. The main drawbacks of these methods are low yields, longer reaction times, high temperature and formation of large number of byproducts. The modern protocol mainly comprises of microwave assisted and phase transfer catalyzed[26-28] pathways to effect the above mentioned reactions to form the coumarin derivatives with considerable yield.

In the present scenario a greener method for the synthesis of organic compounds is necessary, which eliminate or minimize the utilization of non-participating chemicals and reduce the amount of energy, efforts and resources. To a certain extent, the microwave assisted solvent-free synthetic method is a tool to attain this goal. As part of our effort for the synthesis of oxygen heterocycles, we have explored a new microwave assisted approach for the coumarin derivatives.

EXPERIMENTAL

All the chemicals used are of synthetic grade and are obtained from Merck, Sigma-Aldrich, Fluka and used as such. The melting points are determined using a GUNF melting point apparatus by capillary method and are uncorrected. The UV spectra are recorded on Systronic double beam UV-vis spectrophotometer, IR on a Jasco FT/IR- 4100 spectrophotometer by KBr pellet method, NMR spectra recorded on a Bruker Avance DPX 300 MHz spectrometer using TMS as internal standard and Mass spectra recorded on a Shimadzu GC-MS-QP 2010 mass spectrometer. Microwave irradiation is done using a modified Microwave Assisted Reacting System, MARS 1505 (CEM Corporation, USA) and an ELECTROLUX 700 W domestic microwave oven.

Representative procedure for the synthesis of 3-phenyl coumarin (6a): 2-Hydroxybenzaldehyde (1.22 g, 10 mmol), phenylacetic acid (1.36 g, 10 mmol), triethylamine (0.7 mL, 5 mmol) and acetic anhydride (5 mL) are taken in a 50 mL stoppered flask, mixed well and irradiated under 120 W microwave for 5 min intermittently. The reaction mixture is poured into ice-cold water, stirred for 0.5 h at low temperature (0-10 ºC), the separated solid is washed repeatedly with dilute $NaHCO_3$ solution and distilled water, dried and re-crystallized from ethanol. The crystals obtained have more than 90 % purity. The final purification is done with chromatography using a 100-200 mesh silica gel column with light petroleum-ethyl acetate as the eluent by gradient elution method. Melting point, 138-140 ºC. The yield is found to be 88 %.

All other coumarins have been synthesized using the same procedure. Detailed experimental conditions with structure and melting points of the various coumarin derivatives have been tabulated in Tables 1 and 2. The known compounds have been characterized by comparing the melting points and UV, IR, NMR and mass spectrometric data with those of the available literature. The spectroscopic and analytical details of all the new compounds are shown below.

3-(4-Chlorophenyl)-2*H*-chromen-2-one (6c): UV (λ_{max} (nm), methanol) 323, 293, 214; IR (KBr, ν_{max}, cm^{-1}) 3055 (=C-H), 1711 (C=O), 1608 (C=C), 749 (C-Cl); ^{1}H NMR (δ ppm, 300 MHz, $CDCl_3$) 7.80 (s, 1H, =CH), 7.67 (d, *J* = 8.7 Hz, 2H, Ar), 7.54 (d, *J* = 7.5 Hz, 2H, Ar), 7.41 (d, *J* = 8.5 Hz, 2H, Ar), 7.36-7.25 (m, 2H, Ar); ^{13}C NMR (δ ppm, 75 MHz, $CDCl_3$) 160.2, 153.3, 139.8, 134.7, 132.9, 131.5, 129.7, 128.5, 127.8, 126.9, 124.5, 119.3, 116.4; MS (EI) m/z 256.3 (M^+, 100), 228.1 (70), 165.3 (55). Anal. calcd. (%) for $C_{15}H_9O_2Cl$: C, 70.19; H, 3.53; Cl, 13.81. Found. (%): C, 69.83; H, 3.51; Cl, 13.79.

3-(4-Chlorophenyl)-4-methyl-2*H*-chromen-2-one (6g): UV [λ_{max} (nm), methanol] 311, 252, 209; IR (KBr, ν_{max}, cm^{-1}) 1698 (C=O), 1597 (C=C), 775 (C-Cl); ^{1}H NMR (δ ppm, 300 MHz, $CDCl_3$) 7.68 (dd, *J* = 8.1, 1H, Ar), 7.56 (m, 1H, Ar), 7.45-7.24 (m, 6H, Ar), 2.33 (s, 3H, CH_3); ^{13}C NMR (δ ppm, 75 MHz, $CDCl_3$) 160.7, 152.6, 148.0, 134.2, 132.7, 131.6, 131.5, 128.7, 126.1, 125.1, 124.3, 120.3, 116.9, 16.2; MS (EI) m/z 270 (M^+, 100), 241(50), 178(40); Anal. calcd. (%) for $C_{16}H_{11}O_2Cl$: C, 70.99; H, 4.10; Cl, 13.10. Found. (%): C, 71.22; H, 4.08; Cl, 12.98.

3-Cyano-4-methyl-2*H*-chromen-2-one (6h): UV [λ_{max} (nm), methanol] 323, 293, 214; IR (KBr, ν_{max}, cm^{-1}) 2229 (CN), 1724 (C=O), 1602.85 (C=C); ^{1}H NMR (δ ppm, 300 MHz, $CDCl_3$) 7.77 (m, 2H, Ar), 7.47 (m, 2H, Ar), 2.78 (s, 3H, CH_3); ^{13}C NMR (δ ppm, 75 MHz,$CDCl_3$) 162.3, 158.6 154.2, 135, 125.9, 125.4, 119, 118.1, 113.1, 102, 18.2; MS(EI) m/z 185 (M^+, 100), 156 (47), 140 (35), 102 (45); anal. calcd. (%) for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found. (%): C, 70.96; H, 3.79; N ,7.61.

7-Acetoxy-4-methyl-3-phenyl-2*H*-chromen-2-one (9a): UV [λ_{max} (nm), methanol] 369, 311, 207; IR (KBr, ν_{max}, cm^{-1}) 1761 (ester C=O), 1714 (coumarin C=O), 1608 (C=C); ^{1}H NMR (δ ppm, 300 MHz, DMSO-d_6) 7.67 (d, *J* = 8.7, 1H, Ar), 7.47-7.37 (m, 3H, Ar), 7.27 (d, *J* = 10, 2H, Ar), 7.14-7.05 (m, 2H, Ar), 2.35 (s, 3H, CH_3CO), 2.31 (s, 3H, CH_3); ^{13}C NMR (δ ppm, 75 MHz, DMSO-d_6) 169.3, 161.2, 153.6, 153.0, 147.6, 134.6, 130.4, 128.9, 128.7, 127.2, 126.4, 118.6, 110.6, 21.6, 17.1; MS(EI) m/z 294 (M^+, 25), 252 (100), 224 (75); anal. calcd. (%) for $C_{18}H_{14}O_4$: C, 73.46, H, 4.79. Found. (%): C, 73.59; H, 4.81.

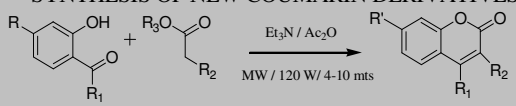
7-Acetoxy-3-phenyl-2*H*-chromen-2-one (9b): UV [λ_{max} (nm), DMSO] 328, 300; IR (KBr, ν_{max}, cm^{-1}) 1751.2 (ester C=O), 1704.9 (coumarin C=O), 1612.3 (C=C); ^{1}H NMR (δ ppm, 300 MHz, DMSO-d_6) 7.81 (s, 1H, =CH), 7.71-7.68 (dd, 2H, Ar), 7.56 (d, 1H, Ar), 7.49-7.41 (m, 3H, Ar), 7.16 (d, , 1H, Ar), 7.09-7.06 (dd, 1H, Ar), 2.35 (s, 3H, CH_3CO), 2.31 (s, 3H, CH_3); ^{13}C NMR (δ ppm, 75 MHz, DMSO-d_6) 168.7, 160.2, 154.0, 152.7, 139.2, 134.4, 128.9, 128.5, 128.4, 127.7, 118.5,117.4, 110.0, 21.1, 17.1; MS (FAB) m/z 281.3 (M + 1, 20), 238.3 (15), 176.2 (25), 154 (100), 138 (85); Anal. calcd. (%) for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found. (%): C, 73.12; H, 4.29.

7-Acetoxy-3-cyano-2*H*-chromen-2-one (9c): UV [λ_{max} (nm), DMSO] 358, 285; IR (KBr, ν_{max}, cm^{-1}) 2248.6 (C≡N), 1734.7 (C=O), 1613.2 (C=C), 1225.5 (C-O); ^{1}H NMR (δ ppm, 300 MHz, DMSO-d_6) 7.72 (s, 1H, CH), 7.67-7.53 (m, 2H, Ar), 7.33 (d, *J* = 3.4 Hz, 1H, Ar), 2.42 (s, 3H, $COCH_3$); ^{13}C NMR (δ ppm, 75 MHz, DMSO-d_6) 172.7, 158.3, 152.4, 149.9, 129.8, 122.4, 119.6, 118.7, 114.7, 113.6, 99.2, 21.4; MS (FAB) m/z 213.7 (M + 1, 100), 203, 186, 160; anal. calcd. (%) for $C_{12}H_7NO_4$: C, 62.89; H, 3.08; N, 6.11. Found. (%): C, 62.62; H, 3.07; N, 6.08.

TABLE-1
3/4-SUBSTITUTED COUMARINS PREPARED UNDER MICROWAVE IRRADIATION

Comp.	R_1	R_2	R_3	Time of irradiation (min)	Yield (%)	m.p. (ºC)	Lit. m.p. (ºC)
6a	H	C_6H_5	H	6	88	138-140	137-139[17]
6b	H	CN	Et	4	75	180-182	182-184[18]
6d	H	4-NO_2-C_6H_4	H	5	80	263-265	262-264[17]
6e	H	COMe	Et	6	78	118-120	120-122[18]
6f	Me	C_6H_5	H	8	69	149-150	153[17]
6i	Me	2-OMe-C_6H_4	H	7	79	121-122	120[17]

TABLE-2
SYNTHESIS OF NEW COUMARIN DERIVATIVES



Compound	R	R'	R_1	R_2	R_3	Time of irradiation (min)	Yield (%)	m.p. (ºC)
6c	H	H	H	4-Cl-C_6H_4	H	7	90	193-194
6g	H	H	Me	4-Cl-C_6H_4	H	9	71	156-158
6h	H	H	Me	CN	Et	6	61	164-168
9a	OH	$OCOCH_3$	Me	C_6H_5	H	8	62	169-171
9b	OH	$OCOCH_3$	H	C_6H_5	H	5	87	172-175
9c	OH	$OCOCH_3$	H	CN	Et	4	73	135-136
9d	OH	$OCOCH_3$	H	COMe	Et	5	69	159-161

7-Acetoxy-3-acetyl-2*H*-chromen-2-one (9d): UV [λ_{max} (nm), DMSO] 339, 301; IR (KBr, ν_{max}, cm^{-1}) 1766 (ester C=O), 1720 (ring C=O), 1612 (C=C), 1195 (C-O); ^{1}H NMR (δ ppm, 300 MHz, DMSO-d_6) 8.51 (s, 1H, =CH), 7.68 (d, *J* = 8.7 Hz, 1H, Ar), 7.18 (d, *J* = 2.1, 1H, Ar), 7.14 (dd, 1H, Ar), 2.72 (s, 3H, CH_3CO), 2.36 (s, 3H, CH_3COO); ^{13}C NMR (δ ppm, 75 MHz, DMSO-d_6) 195.2, 168.3, 158.9, 156.0, 155.1, 146.9, 131.9, 123.5, 119.1, 115.9, 110.1, 30.5, 21.1; MS (FAB) m/z - 247.4 (M + 1, 10), 176.3 (100), 154 (95), 138 (75); anal. calcd. (%) for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found. (%): C, 63.68; H, 4.11.

RESULTS AND DISCUSSION

Triethylamine in combination with other reagents like sodium acetate[13], $PhPOCl_2$[29], 2-chloro-1-methylpyridinium iodide[30], *etc*., has proved to be good catalyst for coumarin formation. A conventional reflux method for the formation of coumarins using triethylamine and acetic anhydride was reported earlier[17]. A remarkable procedural modification from the conventional route, utilizing the flexibility of microwave assisted reaction and the same reagents as catalyst with some interesting results has been successfully explored here. Compared to the early reported conventional protocol, the newly modified microwave assisted method is fast, easy and clean with least number of byproducts and significant yield.

In the present study, a solvent free one-pot strategy for the synthesis of coumarin derivatives under microwave-assisted conditions has been explored. When 2-hydroxy benzaldehyde (**1**) was mixed with phenyl acetic acid (**2**) in the presence of triethylamine and acetic anhydride and irradiated under microwave for 6 min in the absence of a solvent, an efficient reaction occurred and on subsequent work up gave one product that has been identified as 3-phenylcoumarin (**3**). The reaction is represented in the Fig. 1.

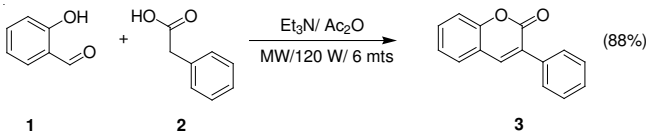
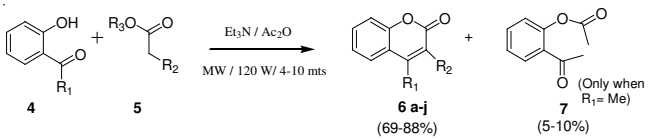


Fig. 1. Synthesis of 3-phenylcoumarin

The reaction is further extended to other substituted acetic acids and their derivatives and 2-hydroxy aromatic aldehydes/ ketones for the synthesis of substituted coumarins (Fig. 2). 3, 4- and 7-substituted coumarins have been synthesized using this fast one-pot protocol.

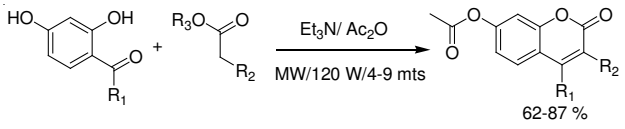


R_1= H , CH_3 , R_2 = H, CN, Cl, C_6H_5, 2-Cl-C_6H_4, 4-NO_2-C_6H_4 , 2-OMe-C_6H_4, COMe, R_3 = H, Et

Fig. 2. Microwave accelerated coumarin synthesis under solvent free condition

In order to prove the concept and versatility of the new protocol many known coumarins were synthesized and characterized by comparing their melting points and spectroscopic data with those reported in the literatures (Table-1).

Interesting observations have been made when 2-hydroxy acetophenone and its derivatives are used as the carbonyl counterpart in the above reaction. When 2-hydroxy acetophenone is used, the yield is comparatively low and 2-acetoxy-acetophenone (**7**) has been formed as the byproduct. Also when 2,4-dihydroxyacetophenone is made to react with the acetic acid derivatives, 7-acetoxy coumarin derivatives have been formed instead of the 7-hydroxy derivatives (Fig. 3).



R_1= H , CH_3 , R_2 = H, CN, Cl, C_6H_5, 2-Cl-C_6H_4, 4-NO_2-C_6H_4 , 2-OMe-C_6H_4, COMe, R_3 = H, Et

Fig. 3. Synthesis of 7-acetoxy-3 and/or 4-substituted coumarin derivatives

The new acetoxy coumarins derivatives synthesized using the novel synthetic protocol is shown in Table-2. All the compounds are characterized using the UV, IR, NMR and mass spectroscopic techniques. The spectroscopic and elemental analysis data of the newly synthesized coumarins are shown in experimental section.

In the absence of acetic anhydride the reaction failed to yield the desired products. Also when the amount of acetic anhydride is reduced to half, the reaction did not proceed to completion. Thus, acetic anhydride is supposed to act as a dehydrating agent, enhancing the rate of condensation of carbonyl compound with active methylene species.

Conclusion

The new method that is contrived by us is an environmentally benign method, as it does not involve the use of toxic volatile organic solvents to a greater extent. This simple protocol can be employed for the expeditious one-pot synthesis of 3-phenyl, 3-cyano, 3-chloro, 3-amino, 3-acetyl, 4-methyl and 7-acetoxy coumarin derivatives, which are very versatile platforms for many synthetic conversions to form high potential pharmacophores. Thus the new protocol paves the way to synthesize multifunctionalized coumarin derivatives by an easy and fast one-pot reaction.

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REFERENCES

1. C.H. Stammer, E. Walton, A.N. Wilson, R.W. Walker, N.R. Trenner, F.W. Holly and Karl Folkers, *J. Am. Chem. Soc*., **80**, 137 (1958).
2. N.A. Gormley, G. Orphanides, A. Meyer, P.M. Cullis and A. Maxwell, *Biochemistry*, **35**, 5083 (1996).
3. H. Chen and C.T. Walsh, *Chem. Biol*., **8**, 301 (2001).

4. A.A. Basile, S. Sorbo, V. Spadaro, M. Bruno, A. Maggio, N. Faraone and S. Rosselli, *Molecules*, **14**, 939 (2009).
5. G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis and D.J. Hadjipavlou-Litina, *Eur. J. Med. Chem*., **44**, 3020 (2009).
6. T. Okamoto, T. Kobayashi and S. Yoshida, *Curr. Med. Chem*., **5**, 47 (2005).
7. R.W. Fuller, H.R. Bokesch, K.R. Gustafson, T.C. McKee, J.H. Cardellina, J.B. McMahon, G.M. Cragg, D.D. Soejarto and M.R. Boyd, *Bioorg. Med. Chem. Lett*., **4**, 1961 (1994).
8. C. Sproll, W. Ruge, C. Andlauer, R. Godelmann and D.W. Lachenmeier, *Food Chem*., **109**, 462 (2008).
9. M. Zahradnik, The Production and Application of Fluorescent Brightening Agents, Wiley & Sons (1992).
10. A. Dorlars, C.W. Schellhammer and J. Schroeder, *Angew. Chem. Int. Ed*., **14**, 665 (2003).
11. G. Jones II and M.A. Rahman, *J. Phys. Chem*., **98**, 13028 (1994).
12. J.D. Hepworth, C.D. Gabbut and B.M. Heron, Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, edn. 2 (1996).
13. W.H. Perkin, *J. Chem. Soc*., **21**, 53 (1868).
14. H. Von Pechmann and C. Duisberg, *Ber. Dtsch. Chem. Ges*., **16**, 2119 (1883).
15. B.T. Watson and G.E. Christiansen, *Tetrahedron Lett*., **39**, 6087 (1998).
16. S. Abbas, V. Hassan and M.H. Majid, *Phosphorus Sulfur Silicon Rel. Elem*., **178**, 501 (2003).
17. K.K. Vijayan, *Indian J. Heterocycl. Chem*., **8**, 10 (1998).
18. D. Bogdal, *J. Chem. Res. (S)*, 468 (1998).
19. V. Singh, J. Singh, P. Kaur and G.L. Kad, *J. Chem. Res. (S)*, 58 (1997).
20. G. Smitha and Ch. Sanjeeva Reddy, *Synth. Commun*., **34**, 3997 (2004).
21. B. Rajithaa, V.N. Kumara, P. Someshwara, J.V. Madhava, P.N. Reddy and Y.T. Reddy, *ARKIVOC*, **12**, 23 (2006).
22. B. Tyagi, M.K. Mishra and R.V. Jasra, *J. Mol. Catal. A: Chem.*, **276**, 47 (2007).
23. N.N. Karade, S.V. Gampawar, S.V. Shinde and W.N. Jadhav, *Chin. J. Chem*., **25**, 1686 (2007).
24. R.D.H. Murray and Z.D. Jorge, *Tetrahedron*, **40**, 3133 (1984).
25. R.D.H. Murray and Z.D. Jorge, *Tetrahedron*, **39**, 3163 (1983).
26. D.M.P. Mingos and D.R. Baghurst, *Chem. Soc. Rev*., **20**, 1 (1991).
27. A.A. Avetisyan, I.L. Aleksanyan and A.G. Alvandzhyan, *Chem. Heterocycl. Comp*., **32**, 773 (1996).
28. H. Ammar, S. Abid and S. Fery-Forgues, *Dyes Pigm*., **78**, 1 (2008).
29. D.J. Gallastegui, J.M. Lago and C. Palomo, *J. Chem. Res. (S)*, 170 (1984).
30. S.H. Mashraqui, D. Vashi and H.D. Mistry, *Synth. Commun*., **34**, 3129 (2004).