One pot synthesis of 3-[2-(arylamino)thiazol-4-yl]coumarins in a three-component synthesis and a catalyst and solvent-free synthesis on grinding

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An efficient synthesis of 3-[2-(arylamino)thiazol-4-yl]coumarins in excellent yields are described. Reaction of 3-(2-bromoacetyl)coumarin with potassium thiocyanate and arylamines, in alcohol resulted in the formation of title compounds in one pot. The same compounds were also prepared by grinding these coumarins and arylthiourea together.

Keywords: 3-(2-bromoacetyl)coumarin, potassium thiocyanate, arylamine, 1-aryl thiourea

Coumarin and its derivatives widely occur in nature and have attracted intense interest in recent years because of their diverse pharmacological properties. Coumarin and its derivatives exhibit several medicinal applications[1] such as anticoagulants, antifungal, insecticidal, ant helminthes, hypnotics, HIV protease inhibitors, AChE inhibitors,[2] and as inhibitors of thrombin and Factor Xa.[3] They have also found applications as photochromes with modulated fluorescence[4,5] and laser dyes.[6]

It is well-known that the substituted thiazolyl group is of great importance in biological systems. A large number of thiazoles obtained from microbial and marine life exhibit important biological effects[7] such as antitumour, antifungal, antibiotic and antiviral activities. Synthetically prepared substituted thiazoles possess a wide range of pharmacological properties[8–10] including Src family kinase inhibitor,[11] antitumour[12] and **antimicrobial**.[13] Their other applications include liquid crystals[14] and cosmetic sunscreens.[15]

In view of the pharmacological, biochemical properties and therapeutic applications of substituted coumarins and thiazoles, we looked for an efficient preparation under mild conditions of thiazolylcoumarin derivatives because of their wide range of medicinal applications.[16,17] These compounds can also be used as novel photochromes.[18] The development of libraries of substituted thiazolylcoumarins might provide additional lead molecules for use in drug reasearch.

2-Aminothiazoles can be synthesised cleanly and in high yields from α-bromoketone and a thiourea via the Hantzsch thiazole synthesis.[19–21] Recently, Moriarty and Prakash reported an efficient modification that utilises α-tosyloxy ketones in place of α-halo carbonyl compounds.[22,23] These methods give excellent yields for simple thiazoles. However, for some substituted thiazoles low yields have been reported as a result of dehalogenation of the α-haloketone during the reaction. So notwithstanding the Hantzsch process and other methods, we required a flexible route that would give high yield and rapid access. In recent years, solid state reactions by grinding have been reported.[24–28] Most of these reactions are carried out at room temperature in a solvent-free environment using only a mortar and pestle, therefore the common merit of these processes is that they are efficient, economical, and environmentally friendly. In continuation of our earlier work on the synthesis of heterocyclic systems derived from coumarins,[29–32] we report here a synthesis of substituted 3-[2-(arylamino)-thiazol-4-yl] coumarins in two methods. Method 1 involves one-pot three-component reaction and method 2 is solid state grinding.

Results and discussions

In method 1 (Scheme 1), an equimolar mixture of 3-(2-bromoacetyl)coumarin and potassium thiocyanate in ethanol gave 3-(2-thiocyanatoacetyl)coumarin which on subsequent addition of arylamine undergoes a nucleophilic addition followed by intra molecular cyclisation and subsequent dehydration resulted in the formation of compound **4**. It is conceivable that the formation of **4** from **1** and **8** occurs in two stages. Thus, **4** may be formed from **1** and **8** by an initial reaction with potassium thiocyanate leading to the formation of **6** and **9** respectively, followed by its reaction with substituted anilines giving **4**.

Method 2 (Scheme 2) is a solid state synthesis. In this method, equimolar amounts of 3-(2-bromoacetyl)coumarin and 1-arylthiourea on grinding at room temperature under catalyst and solvent-free condition gave **4**. However, the problem with the grinding reaction is that the starting materials soon become a tough waxy substance that is hard to grind. To over come this, we added three drops of water to the mixture until the substance form a-paste-like product that was easily ground. The overall yields of the products obtained by both methods are reported in Table 1. From the results we found that solvent-free method has advantage over conventional solvent reaction for the preparation of **4**. The products obtained from both methods were found to be identical by mixed m. p. measurements, co TLC and spectral data.

The IR spectrum of compound **4a** shows prominent peaks at 1607 (–C=N), 1708 (lactone C=O), and a sharp peak of (–NH) at 3307 cm^{-1}. The ^1H NMR of compound **4a** shows a characteristic singlet for $–CH_3$ at δ 2.27, C_4 proton of coumarin appeared at δ 8.60 as a singlet and NH proton showed a singlet at δ 9.85. The remaining protons were observed in the usual region. *N*-Acylation of compound **4a** with acetic anhydride and catalytic amount of pyridine gave the compound **5** (Scheme 3). The proton NMR of compound **5** shows a characteristic singlet for carbonyl attached $–CH_3$ at δ 2.51 indicates the absence of NH proton in the compound **5**.

Experimental

All the reagents and solvents were pure, purchased from commercial sources and were used without further purification unless other wise stated. 3-(2-Bromoacetyl)coumarins,[33] 3-(2- thiocyanatoacetyl)coumarins[34] were prepared by literature procedure. Melting points were determined in open capillaries with a "Cintex" melting point apparatus Mumbai, India and were uncorrected. CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyser. The purity of the compounds was checked by TLC plates (E. Merek Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^1H NMR spectra were recorded on a Bruker WM-300 spectrometer in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

*General procedure for the synthesis of substituted 3-[2-(arylamino)thiazol-4-yl]coumarins (***4a–m***)*

Method (**a**): A mixture of 3-(2-bromoacetyl)coumarin (1 mmol) and potassium thiocyanate (1 mmol) was taken in 10 mL ethanol stirred at

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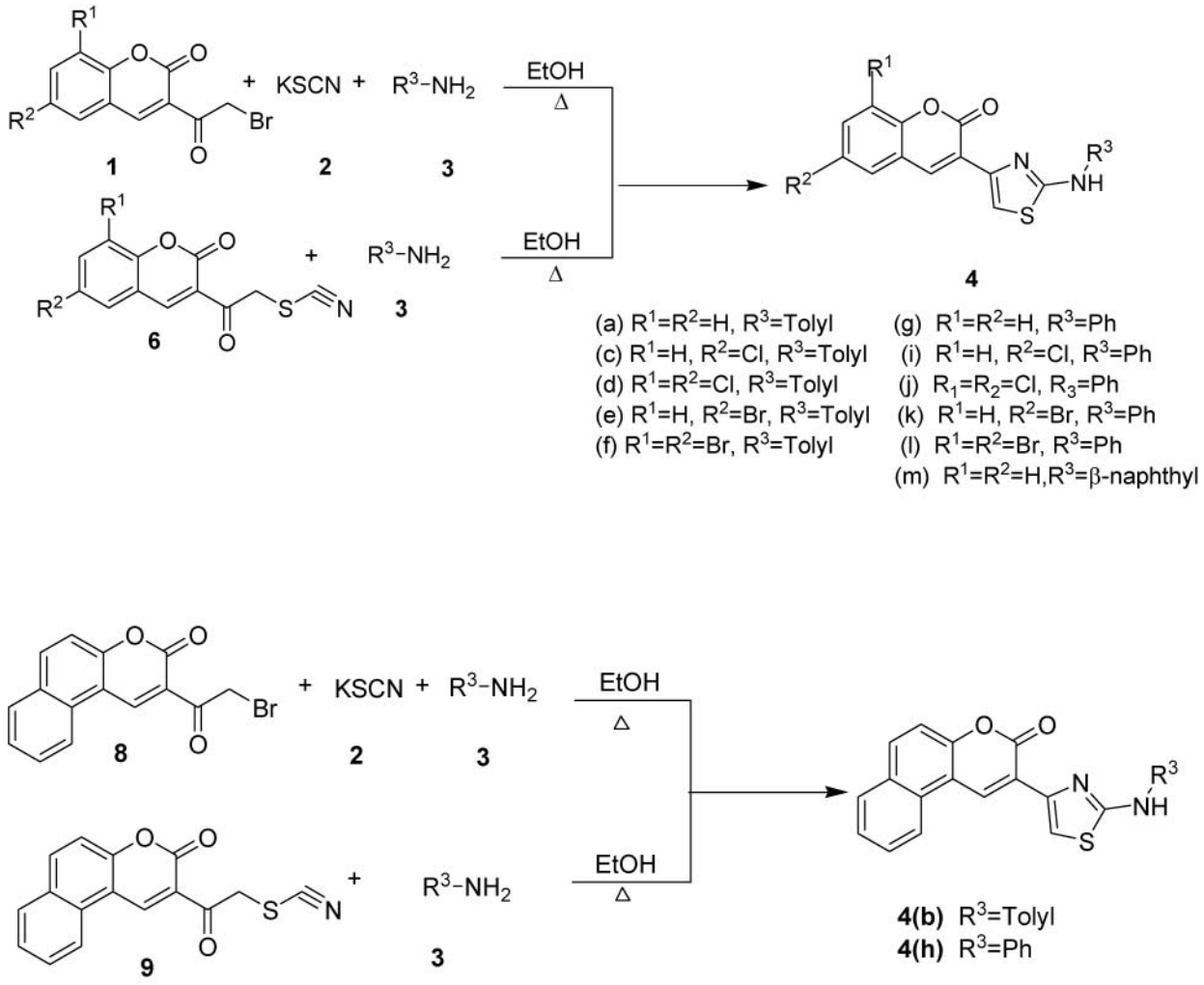
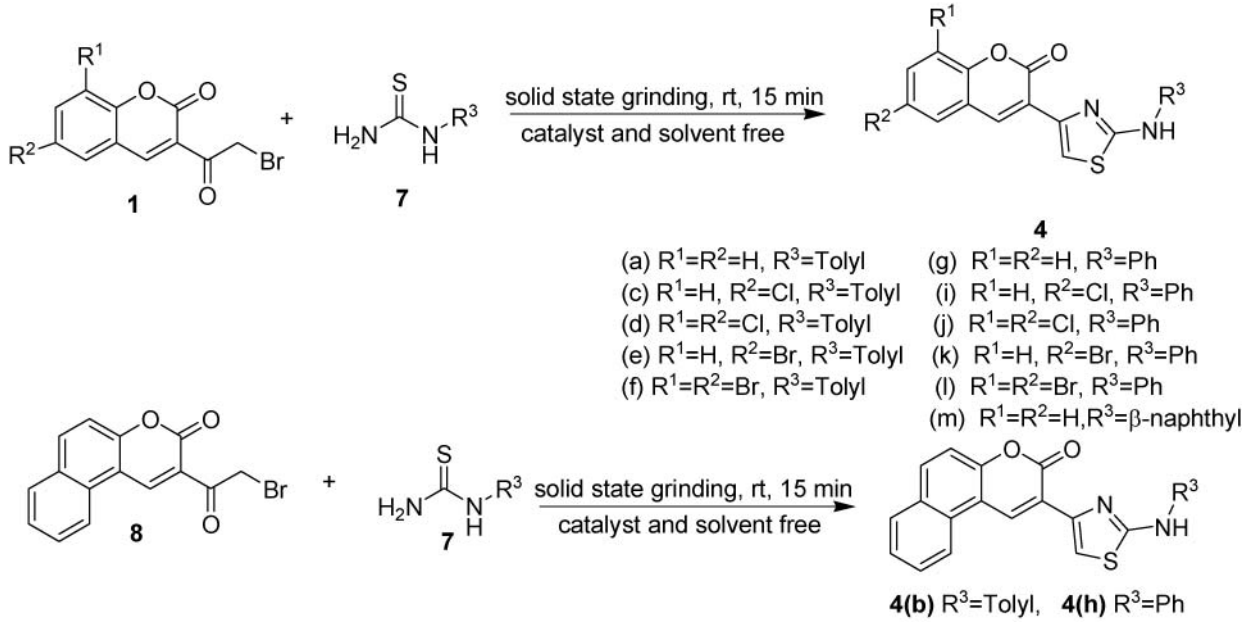


Scheme 1 Synthesis of 3-[2-(arylamino)thiazol-4-yl]coumarins by one pot (Method 1).



Scheme 2 Synthesis of 3-[2-(arylamino)thiazol-4-yl]coumarins by grinding.

room temperature for 1h. After completion of the reaction 1.2 mmol of arylamine was added and stirred at 60–65 °C for 2h. The reaction mass was cooled, the yellow solid product obtained was filtered under reduced pressure and recrystallised from ethanol. All the other compounds were prepared similarly.

Method (**b**): A mixture of 3-(2-bromoacetyl)coumarin (1 mmol) and 1-arylthiouea (1 mmol) was taken in a mortar, grinded vigorously for 15 min by adding 2–3 drops of water. After completion of the reaction, the product was recrystallised from ethanol. All the other compounds were prepared similarly.

Table 1 The overall % of yields of compounds **4a-m** in both solvent and solvent-free methods are as follows

Entry	Solvent method	Solvent-free method
4a	80	89
4b	85	91
4c	83	87
4d	85	90
4e	82	89
4f	87	87
4g	75	85
4h	70	85
4i	74	87
4j	80	92
4k	76	89
4l	75	86
4m	85	94

General procedure for preparation of **4** *from 3-(2-thiocyanatoacetyl) coumarins*

A mixture of 3-(2-thiocyanatoacetyl)coumarin (1mmol) and arylamine (1mmol) was taken in 10 mL ethanol stirred at 60–65 °C for 2h. After completion of the reaction, the product formed was filtered, washed with ethanol and recrystallised from ethanol.

N-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]-N-p-tolylacetamide (**5**): 3-[2-(*p*-Tolylamino)thiazol-4-yl]-2*H*-chromen-2-one (**4a**) (1 mmol) was taken in 3 mL of acetic anhydride and catalytic amount of pyridine was added, the mixture was heated at 50–55 °C for 5–10 min and kept aside for 16 h. The crude yellow crystalline solid obtained was filtered, washed with water and recrystallised from ethanol.

*Spectral data for substituted 3-[2-(arylamino)thiazol-4-yl]coumarins (***4a–m***) and its acetyl derivative* **5**

*3-[2-(*p-*Tolylamino)thiazol-4-yl]-*2H-*chromen-2-one* (**4a**): Yellow solid, M.p. 184–185 °C. IR (KBr, ν_{max} cm^{-1}): 1538 (C=C), 1607 (–C=N), 1708 (lactone –C=O), 3307 (-NH). ^{1}H NMR (DMSO-d_6 δ ppm): 2.27 (s, 3H, CH_3), 7.13–7.17 (m, 2H, ArH), 7.29–7.35 (m, 2H, ArH), 7.50–7.59 (m, 3H, ArH), 7.50–7.80 (m, 2H, 1H of thiazole and 1H of ArH), 8.60 (s, 1H, C_4 of coumarin), 9.85 (s, 1H, NH, D_2O, exchangeable). ^{13}C NMR ($CDCl_3$ δ ppm): 20.79, 109.88, 116.27, 119.17, 119.59, 120.86, 124.48, 128.22, 130.03, 131.21, 133.38, 137.59, 138.74, 143.97, 152.83, 159.70 and 164.63. EI-MS 335 [M+H]$^+$. Anal. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22; N, 8.38; S, 9.59. Found: C, 68.21; H, 4.18; N, 8.40; S, 9.52%.

*2-[2-(*p-*Tolylamino)thiazol-4-yl]-3*H-*benzo[f]chromen-3-one* (**4b**): Yellow solid, M.p. 243–244 °C. IR (KBr, ν_{max} cm^{-1}): 1545 (C=C), 1605 (–C=N), 1708 (lactone –C=O), 3310 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 2.31 (s, 3H, CH_3), 7.24–7.26 (m, 2H, ArH), 7.87–7.89 (m, 2H, ArH), 8.10–8.40 (m, 7H, 1H, of thiazole and 6H of ArH), 8.72 (s, 1H, C_4 of coumarin), 10.33 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{23}H_{16}N_2O_2S$: C, 71.85; H, 4.19; N, 7.29; S, 8.34. Found: C, 71.81; H, 4.16; N, 7.25; S, 8.31%.

*3-[2-(*p-*Tolyamino)thiazol-4-yl]-6-chloro-*2H-*chromen-2-one* (**4c**): Yellow solid, M.p. 202–203 °C. IR (KBr, ν_{max} cm^{-1}): 1546 (C=C), 1603 (–C=N), 1713 (lactone –C=O), 3320 (–NH). ^{1}H NMR ($CDCl_3$ δ ppm): 2.35 (s, 3H, CH_3), 7.19–7.31 (m, 6H, ArH), 7.45 (d, 1H, *J* = 6Hz, ArH) 7.55 (s, 1H, thiazole), 7.86 (s, 1H, C_4 of coumarin), 8.47 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{19}H_{13}ClN_2O_2S$: C, 61.87; H, 3.55; N, 7.60; S, 8.69. Found: C, 61.83; H, 3.51; N, 7.54; S, 8.64%.

*3-[2-(*p-*Tolylamino)thiazol-4-yl]-6,8-dichloro-2*H-*chromen-2-one* (**4d**): Yellow solid, M.p. 208–209 °C. IR (KBr, ν_{max} cm^{-1}): 1546 (C=C), 1607 (–C=N), 1704 (lactone –C=O), 3280 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 2.28 (s, 3H, CH_3), 7.19 (d, 2H, *J* = 6 Hz, ArH), 7.49 (d, 1H, *J* = 6 Hz, ArH), 7.63–7.66 (m, 2H, ArH), 7.78 (s, 1H, ArH), 8.15 (s, 1H, thiazole), 8.66 (s, 1H, C_4 of coumarin), 10.25 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{19}H_{12}Cl_2N_2O_2S$: C, 56.59; H, 3.00; N, 6.95; S, 7.95. Found: C, 56.54; H, 2.96; N, 6.91; S, 7.91%.

*3-[2-(*p-*Tolyamino)thiazol-4-yl]-6-bromo-*2H-*chromen-2-one* (**4e**): Yellow solid, M.p. 196–197 °C. IR (KBr, ν_{max} cm^{-1}): 1548 (C=C), 1606 (–C=N), 1732 (lactone –C=O, 3321 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 2.28 (s, 3H, CH_3), 7.19 (d, 2H, *J* = 6 Hz, ArH), 7.43 (d, 1H, *J* = 6 Hz, ArH), 7.65 (d, 2H, *J* = 6 Hz, ArH), 7.76 (t, 2H, *J* = 6Hz, ArH), 8.29 (s, 1H, thiazole), 8.65 (s, 1H, C_4 of coumarin), 10.26 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{19}H_{13}BrN_2O_2S$: C, 55.22; H, 3.17; N, 6.78; S, 7.76. Found: C, 55.18; H, 3.14; N, 6.74; S, 7.72%.

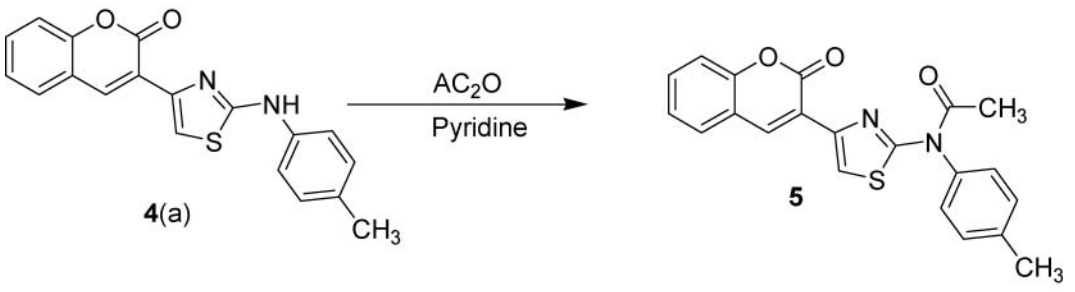
*3-[2-(*p-*Tolylamino)thiazol-4-yl]-6,8-dibromo-2*H-*chromen-2-one* (**4f**): Yellow solid, M.p. 220–222 °C. IR (KBr, ν_{max} cm^{-1}): 1550 (C=C), 1603 (–C=N), 1726 (lactone –C=O), 3319 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 2.28 (s, 3H, CH_3), 7.19 (d, 2H, *J* = 6 Hz, ArH), 7.65 (d, 2H, *J* = 6 Hz, ArH), 7.79 (s, 1H, ArH), 8.13 (s, 1H, ArH), 8.32 (s, 1H, thiazole), 8.61 (s, 1H, C_4 of coumarin), 9.93 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{19}H_{12}Br_2N_2O_2S$: C, 46.37; H, 2.46; N, 5.69; S, 6.51. Found: C, 46.31; H, 2.42; N, 5.62; S, 6.48%.

*3-[2-(Phenylamino)thiazol-4-yl]-2*H-*chromen-2-one* (**4g**): Yellow solid, M.p. 246–247 °C. IR (KBr, ν_{max} cm^{-1}): 1536 (C=C), 1609 (–C=N), 1705 (lactone –C=O), 3308 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 6.96 (t, 1H, *J* = 7 Hz, ArH), 7.30–7.38 (m, 4H, ArH), 7.55 (t, 1H, *J* = 7 Hz, ArH), 7.66–7.73 (m, 3H, ArH), 7.75 (s, 1H, thiazole), 8.60 (s, 1H, C_4 of coumarin), 9.85 (s, 1H, NH, D_2O, exchangeable). EI-MS 321 [M+ H]$^+$. Anal. Calcd for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74; S, 10.01. Found: C, 67.46; H, 3.71; N, 8.64; S, 9.98%.

*2-[2-(Phenylamino)thiazol-4-yl]-3*H-*benzo[f]chromen-3-one* (**4h**): Yellow solid, M.p. 202–203 °C. (KBr, ν_{max} cm^{-1}): 1547(C=C), 1604 (–C=N), 1726 (lactone –C=O), 3310 (–NH).^{1}H NMR (DMSO-d_6 δ ppm): 7.02 (t, 1H, *J* = 6 Hz, ArH), 7.45 (t, 2H, *J* = 6 Hz, ArH),7.64–7.70 (m, 3H, ArH), 7.78–7.80 (m, 4H, ArH), 8.11 (d, 1H, *J* = 6 Hz, ArH), 8.46 (s, 1H, thiazole), 8.74 (s, 1H, C_4 of coumarin), 10.44 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{22}H_{14}N_2O_2S$: C, 71.33; H, 3.81; N, 7.56; S, 8.66. Found: C, 71.30; H, 3.79; N, 7.52; S, 8.62%.

*3-[2-(Phenylamino)thiazol-4-yl]-6-chloro-*2H-*chromen-2-one* (**4i**): Yellow solid, M.p. 168–170 °C. IR (KBr, ν_{max} cm^{-1}): 1546 (C=C), 1604 (–C=N), 1720 (lactone –C=O), 3358 (–NH). ^{1}H NMR ($CDCl_3$ δ ppm): 7.10–7.14 (m, 1H, ArH), 7.40–7.43 (m, 4H, ArH), 7.59 (t, 1H, *J* = 6 Hz, ArH), 7.61–7.73 (m, 2H, ArH), 7.78 (s, 1H, thiazole), 8.41 (s, 1H, C_4 of coumarin), 8.48 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{18}H_{11}ClN_2O_2S$: C, 60.93; H, 3.12; N, 7.90; S, 9.04. Found: C, 60.90; H, 3.15; N, 7.86; S, 9.10%.

*3-[2-(Phenyamino)thiazol-4-yl]-6,8-dichloro-2*H-*chromen-2-one* (**4j**): Yellow solid, M.p. 172–173 °C. IR (KBr, ν_{max} cm^{-1}): 1545 (C=C), 1602 (–C=N), 1720 (lactone –C=O), 3354 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 7.01–7.81 (m, 7H, ArH), 8.16 (s, 1H, thiazole), 8.68 (s, 1H, C_4 of coumarin), 10.37 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{18}H_{10}Cl_2N_2O_2S$: C, 55.54; H, 2.59; N, 7.20; S,8.24. Found: C, 55.51; H, 2.54; N, 7.15; S, 8.21%.



Scheme 3 N-acetylation of compound **4a**.

*3-[2-(Phenylamino)thiazol-4-yl]-6-bromo-2*H-*chromen-2-one* (**4k**): Yellow solid, M.p. 178–179 °C. IR (KBr, ν_{max} cm^{-1}): 1546 (C=C), 1602 (–C=N), 1724 (lactone –C=O), 3314 (–NH). ^{1}H NMR ($CDCl_3$ δ ppm): 7.11–7.48 (m, 8H, ArH), 7.59 (s, 1H, thiazole), 7.90 (s, 1H, C_4 of coumarin), 8.50 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{18}H_{11}BrN_2O_2S$: C, 54.15; H, 2.78; N, 7.02; S, 8.03 . Found: C, 54.10; H, 2.78; N, 7.00; S, 8.00%.

*3-[2-(Phenyamino)thiazol-4-yl]-6,8-dibromo-2*H-*chromen-2-one* (**4l**): Yellow solid, M.p. 245–246 °C. IR (KBr, ν_{max} cm^{-1}): 1542 (C=C), 1606 (–C=N), 1719 (lactone –C=O), 3359 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 7.01 (t, 1H, *J* = 6 Hz, ArH), 7.38 (t, 2H, *J* = 6 Hz, ArH), 7.77–7.83 (m, 3H, ArH), 8.13 (s, 1H, ArH), 8.34 (s, 1H, thiazole), 8.65 (s, H, C_4 of coumarin), 10.39 (s, 1H, NH, D_2O, exchangeable). Anal. Calcd for $C_{18}H_{10}Br_2N_2O_2S$: C, 45.21; H, 2.11; N, 5.86; S, 6.71. Found: C, 45.00; H, 2.00; N, 5.83; S, 6.67%.

*3-[2-(Naphthalene-3-ylamino)thiazol-4-yl]-2*H-*chromen-2-one* (**4m**): Yellow solid, M.p. 267–268 °C. IR (KBr, ν_{max} cm^{-1}): 1518 (C=C), 1592 (–C=N), 1719 (lactone –C=O), 3150 (–NH). ^{1}H NMR (DMSO-d_6 δ ppm): 7.26–7.37 (m, 3H, ArH), 7.47–7.55 (m, 4H, ArH), 7.62–7.75 (m, 4H, ArH), 7.85 (s, 1H, thiazole), 8.72 (s, 1H, C_4 of coumarin), 10.32 (s, 1H, NH, D_2O, exchangeable). EI-MS 371 [M+ H]$^+$. Anal. Calcd for $C_{22}H_{14}N_2O_2S$: C, 71.33; H, 3.81; N, 7.56; S,8.66. Found: C, 71.30; H, 3.78; N, 7.59; S, 8.63%.

N-[4-(2-Oxo-2H-cromen-3-yl]thiazol-2-yl)-N-p-tolyl acetamide (**5**): Yellow solid, yield 80%, M.p. 198–199 °C. IR (KBr, ν_{max} cm^{-1}): 1511 (C=C), 1604 (–C=N), 1675 (–C=O of N-acyl), 1719 (lactone –C=O). ^{1}H NMR ($CDCl_3$ δ ppm): 2.09 (s, 3H, CH_3), 2.51 (s, 3H, CH_3 of N-acyl), 7.23–7.47 (m, 8H, ArH), 8.10 (s, 1H, thiazole), 8.17 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C, 67.00; H, 4.28; N, 7.44; S, 8.52. Found: C, 66.94; H,4.23; N, 7.40; S, 8.48%.

Conclusion

In conclusion, we have developed a simple, mild, inexpensive, fast and efficient one pot synthesis of 3-(2-(arylamino)-4-thiazolyl)coumarins without using any catalyst. The biological activity of these compounds is being studied.

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