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An efficient synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives containing coumarin skeletons via a one-pot, three-component reaction

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Abstract New dialkyl 3-(2-oxo-2*H*-3-chromenylcarbonyl)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate derivatives were prepared by the reaction of 3-(2-bromoacetyl)coumarins, isoquinoline, and dialkyl acetylenedicarboxylates in the presence of triethylamine. This protocol has some advantages such as easy purification, easy performance, and good yields. The structures were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed (Scheme 2).

Keywords 3-(2-Bromoacetyl)coumarin · Dialkyl acetylenedicarboxylate · Pyrrolo[2,1-*a*]isoquinoline · Salicylaldehyde

Introduction

Coumarin cores are one of the most important families of oxygen-containing heterocyclic compounds. They are attractive and versatile molecules that are widely present in microorganisms, animals, and especially in higher plants such as Leguminosae, Thymelaeaceae, Apiaceae, Asteraceae, and Rutaceae [1]. Coumarins have attracted attention due to their antiviral [2, 3], antitumor [4], inhibitor of HIV-1 protease [5], anticholinergic [6], and antipsychotic [7] properties. They have also been used as optical brightening agents, tunable dye lasers, food additives, and in fragrances [8, 9].

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Among them, 3-substituted coumarins are an important class of compounds that are found in some drugs and drug candidates, such as warfarin [10], novobiocin [11], and carbochromen (Fig. 1) [12]. Moreover, electron-accepting substituents at 3-position can improve the fluorescence properties of the coumarins. Due to these important properties, syntheses of new coumarin derivatives have been considered by chemists and a range of methods have been reported for their synthesis [13–22].

The nitrogen-containing heterocycles are important organic scaffolds and they are widely used as key elements in the synthesis of numerous drugs and medicinal agents [23, 24], and they can act as biomimetic and active pharmacophores [25–27]. Among them, pyrrolo[2,1-*a*]isoquinoline skeletons are important heterocyclic systems found in natural products such as lamellarin and crispine alkaloids [28–32], which exhibit antiviral and anticancer activities [33, 34] and are widely used in material science and the drug industry [35, 36]. Due to these properties, they are widely considered in synthetic organic chemistry and various methods have been devised for their synthesis [37–43]. In the course of our research program into the design of new routes for the synthesis of new heterocyclic compounds, we have been interested in the synthesis of heterocyclic compounds with both coumarin and pyrrolo[2,1-*a*]isoquinoline skeleton by a one-pot, three-component reaction.

Experimental

All starting materials were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. 3-acetylcoumarin and 3-(2-bromoacetyl)coumarin were prepared according to published procedures [50, 51]. M.p.: Electrothermal 9100 apparatus. Elemental analyses for C, H, and N: Heraeus CHN–O–Rapid analyzer. Mass spectra: FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., on a BRUKER DRX 500-AVANCE FT-NMR instrument, in $CDCl_3$ if not otherwise stated. IR Spectra: in KBr on a Shimadzu IR-460 spectrometer.

General procedure (exemplified for 3-acetylcoumarin)

A solution of salicylaldehyde (10 mmol, 1,220 mg), methyl acetoacetate (10 mmol, 1,160 mg), and piperidine (0.5 mmol, 42 mg) in EtOH were magnetically stirred for

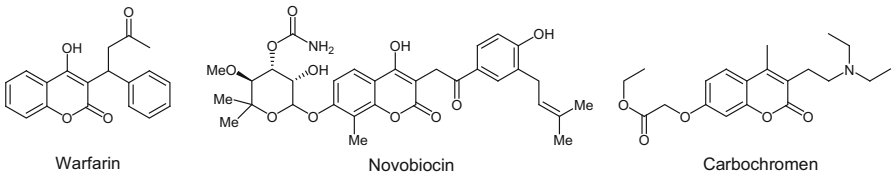


Fig. 1 Some biologically active 3-substituent coumarins

1 h. Then the precipitate was filtered and washed with cold EtOH (10 ml) to afford the pure 3-acetylcoumarin (Scheme 1).

General procedure (exemplified for 1a)

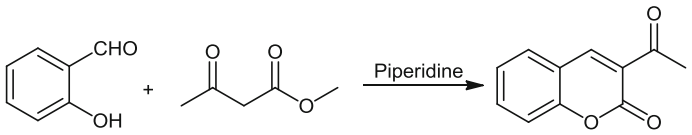
A solution of 3-acetylcoumarin derivatives (10 mmol, 1,880 mg), NBS (11 mmol, 1,958 mg), and *p*-toluenesulfonic acid (1 mmol, 172 mg) in chloroform-acetonitrile (25:5) were magnetically stirred at reflux. After completion of the reaction [about 4 h; TLC (AcOEt/hexane 1:3)], the mixture was cooled and the precipitate was filtered and washed with EtOH (10 ml) to afford the pure product 3-(2-bromoacetyl)coumarin derivatives (Scheme 2).

General procedure (exemplified for 3a)

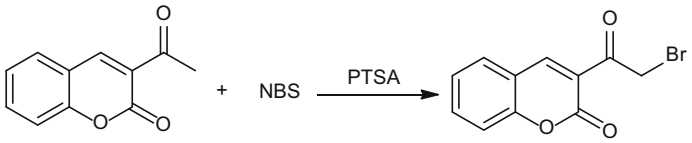
A solution of isoquinoline (1 mmol, 129 mg) and 3-(2-bromoacetyl)coumarin (**1a**) (1 mmol, 266 mg) in acetonitrile (5 ml) were magnetically stirred for 1 h at r.t. Then, triethylamine (1 mmol, 101 mg) was added to the mixture and orange participate was formed. Then, dialkyl acetylenedicarboxylate (1 mmol, 142 mg) was added dropwise to the mixture during 5 min and the solution stirred for 4 h. After completion of the reaction [about 5 h; TLC (AcOEt/hexane 1:3)], the mixture was filtered and the precipitate was washed with EtOH (4 ml) to afford the pure product **3a–i** (Table 1).

Dimethyl 3-[(2-oxo-2H-chromen-3-yl)carbonyl]pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (Table 2, entry a)

Yield: 319 mg (70 %). White powder, M.p. 224 °C (decomp). (KBr, cm^{-1}): 1,203 (C–O), 1,455, 1,508, and 1,625 (Ar), 1,735 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.32 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 7.45 (t, J = 7.4, 1



Scheme 1 Synthesis of 3-acetyl coumarin



Scheme 2 Synthesis of 3-(2-bromoacetyl)coumarin

Table 1 Optimization of the reaction conditions for the formation of **3a**

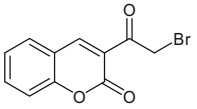
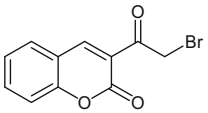
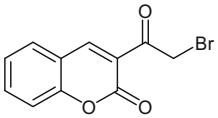
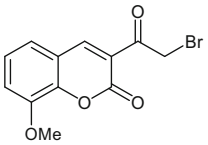
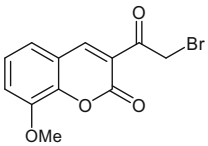
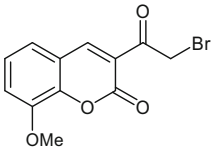
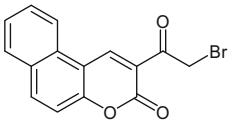
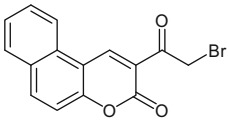
Entry	Catalyst (eq)	Solvent	Time (h)	Yield [%]
1	Et_3N (1)	MeCN	4	70
2	NaOH (1)	MeCN	4	20
3	K_2CO_3 (1)	MeCN	4	30
4	Piperidine (1)	MeCN	4	25
5	Et_3N (1)	DMF	4	60
6	Et_3N (1)	EtOH	4	45
7	Et_3N (1)	$CHCl_3$	4	35
8	Et_3N (0.7)	MeCN	4	45
9	Et_3N (1.2)	MeCN	4	70
10	Et_3N (1)	MeCN	3	55
11	Et_3N (1)	MeCN	5	70

H, CH of Ar); 7.53 (d, $J = 8.4$, 1 H, CH of Ar); 7.63 (d, $J = 7.6$, 1 H, CH^6 of pyrroloisoquinoline); 7.72–7.80 (m, 3H, CH of Ar); 7.82 (dd, $^3J = 8.0$, $^4J = 1.2$, 1 H, CH of Ar); 8.00 (d, $J = 7.2$, 1 H, CH of Ar); 8.46 (s, 1 H, CH^4 of coumarin); 8.87 (d, $J = 8.0$, 1 H, CH of Ar); 9.24 (d, $J = 7.2$, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 52.5; 52.6; 109.3; 116.4; 116.7, 117.7; 121.8; 123.0; 124.0; 125.2; 125.5; 126.3; 127.6; 128.6; 128.7; 129.8; 129.8; 129.9; 132.5; 134.0; 144.4; 153.9; 157.3; 164.5; 164.6; 180.3. MS (EI, 70 eV): 455 (M^+,1), 360 (10), 356 (7), 303 (6), 180 (14), 165 (99), 150 (26), 137 (98), 120 (100), 104 (28), 92 (68), 65 (46). Anal. calc. for $C_{26}H_{17}NO_7$ (455.42): C 68.57, H 3.76, N 3.08; Found: C 68.45, H 3.97, N 3.21.

*Diethyl 3-[(2-oxo-2*H*-chromen-3-yl)carbonyl]pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate* (Table 2, entry b)

Yield: 363 mg (75 %). Pale yellow powder. M.p. 200–202 °C. (KBr, cm^{-1}): 1,202 (C–O), 1,485, 1,507, and 1,611, (Ar), 1,722 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.00 (t, $J = 7.0$, 3 H, OCH_2CH_3);1.27 (t, $J = 7.2$, 3 H, OCH_2CH_3); 3.70 (q, $J = 7.2$, 2 H, OCH_2CH_3); 4.35 (q, $J = 7.0$, 2 H, OCH_2CH_3); 7.45 (td, $^3J = 7.0$, $^4J = 0.8$, 1 H, CH of Ar); 7.52 (d, $^3J = 8.4$, 1 H, CH of Ar); 7.64 (d, $^3J = 7.2$, 1 H, CH^6 of pyrroloisoquinoline); 7.73–7.81 (m, 3 H, CH of Ar); 7.84 (dd, $^3J = 7.8$, $^4J = 1.8$, 1 H, CH of Ar); 8.01 (dd, $^3J = 7.2$, $^4J = 1.6$, 1 H, CH of Ar); 8.47 (s, 1 H, CH^4 of coumarin); 8.87 (d, $J = 7.6$, 1 H, CH of Ar); 9.23 (d, $J = 7.6$, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 13.2; 13.7; 61.4; 61.8; 109.6; 116.38; 116.6; 117.8; 121.8; 123.1; 124.0; 125.2; 125.5; 126.4; 127.6; 128.5; 128.7; 129.8; 129.8; 129.8; 132.4; 134.0; 144.5; 153.9; 157.2; 164.2 (2 CO_2); 180.3. MS (EI, 70 eV): 483 (M^+, 32), 438 (6), 411 (15), 366 (9), 338 (13), 311 (11), 238 (34), 220 (27), 194 (19), 173 (100), 139 (27), 101 (24). Anal. calc. for $C_{28}H_{21}NO_7$ (483.47): C 69.56, H 4.38, N 2.90; Found: C 69.63, H 4.29, N 2.94.

Table 2 Prepared dialkyl 3-[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylates

Entry	Compound 1	R'	Yield [%]
a		Me	70
b		Et	75
c		*t*-Bu	78
d		Me	83
e		Et	86
f		*t*-Bu	91
g		Me	68
h		Et	72
i		*t*-Bu	77

*Di(*tert*-butyl) 3-[(2-oxo-2*H*-chromen-3-yl)carbonyl]pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate* (Table 2, entry c)

Yield: 421 mg (78 %).Yellow powder. M.p. 210–213 °C. (KBr, cm^{-1}): 1,250, 1,210, and 1,156 (C–O), 1,454, 1,508, and 1,611 (Ar), 1723 (br., 4 C=O), ^{1}H NMR

(400 MHz, DMSO-d_6): δ (ppm) = 1.16 (s, 9 H, $OCMe_3$); 1.62 (s, 9 H, $OCMe_3$); 7.44 (t, J = 7.6, 1 H, CH of Ar); 7.51 (d, J = 7.2, 2 H, CH of Ar); 7.73–7.78 (m, 3 H, CH of Ar); 7.87 (dd, ^3J = 7.8, ^4J = 1.4, 1 H, CH of Ar); 8.97 (dd, ^3J = 7.2, ^4J = 2.0, 1 H, CH of Ar); 8.46 (dd, ^3J = 7.2, ^4J = 2.0, 1 H, CH of Ar); 8.53 (s, 1 H, CH^4 of coumarin); 8.97 (d, J = 7.2, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 27.0; 27.7; 82.4; 82.6; 112.2; 115.8; 116.3; 118.1; 121.8; 123.2; 123.9; 124.2; 125.2; 126.7; 127.3; 127.7; 128.3; 128.8; 129.2; 130.0; 131.9; 134.3; 145.7; 154.0; 157.0; 162.6; 164.1; 180.6. MS (EI, 70 eV): 539 (M^+, 13), 483 (6), 427 (57), 383 (13), 338 (10), 238 (24), 211 (100), 194 (43), 166 (39), 148 (53), 120 (52), 91 (58), 56 (74). Anal. calc. for $C_{32}H_{29}NO_7$ (539.58): C 71.23, H 5.42, N 2.60; Found: C 71.11, H 5.49, N 2.57.

*Dimethyl 3-[(8-methoxy-2-oxo-2*H*-chromen-3yl)-carbonyl]pyrrolo [2,1-*a*]isoquinoline-1,2-dicarboxylate* (Table 2, entry d)

Yield: 403 mg (83 %). Beige powder. M.p. 250–252 °C. (KBr, cm^{-1}): 1,202 and 1,272 (C–O), 1,472, and 1,619 (Ar), 1,728 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.33 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 3.97 (s, 3 H, OMe); 7.34–7.40 (m, 2 H, CH of Ar); 7.45 (dd, ^3J = 7.8, ^4J = 2.2, 1 H, CH of Ar); 7.65 (d, J = 7.6, 1 H, CH^6 of pyrroloisoquinoline); 7.74 (td, ^3J = 7.0, ^4J = 1.6, 1 H, CH of Ar); 7.79 (td, ^3J = 7.0, ^4J = 1.6, 1 H, CH of Ar); 8.01 (dd, ^3J = 8.0, ^4J = 1.6, 1 H, CH of Ar); 8.44 (s, 1 H, CH^4 of coumarin); 8.88 (d, ^3J = 8.0, 1 H, CH of Ar); 9.24 (d, ^3J = 7.6, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 52.5; 52.6; 56.2; 109.3; 116.0; 116.7; 118.3; 120.7; 121.8; 123.1; 124.0; 125.1; 125.5; 126.4; 127.6; 128.6; 129.8; 129.9; 130.6; 132.5; 143.2; 144.6; 146.4; 157.0; 164.5; 164.6; 180.3. MS (EI, 70 eV): 485 (M^+, 74), 454 (14), 426 (19), 310 (26), 252 (30), 193 (100), 164 (80), 129 (69), 115 (39), 89 (62), 76 (61). Anal. calc. for $C_{27}H_{19}NO_8$ (485.45): C 66.80, H 3.94, N 2.89; Found: C 66.93, H 4.04, N 2.96.

*Diethyl 3-[(8-methoxy-2-oxo-2*H*-chromen-3-yl)carbonyl]pyrrolo [2,1-*a*]isoquinoline-1,2-dicarboxylate* (Table 2, entry e)

Yield: 442 mg (86 %). Pale yellow powder. M.p. 200 °C (decomp). (KBr, cm^{-1}): 1,203 and 1,274 (C–O), 1,467, and 1,616 (Ar), 1,725 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.00 (t, ^3J = 7.2, 3 H, OCH_2CH_3); 1.27 (t, J = 7.2, 3 H, OCH_2CH_3); 3.70 (q, J = 7.2, 2 H, OCH_2CH_3); 3.96 (s, 3 H, OMe); 4.35 (q, J = 7.2, 2 H, OCH_2CH_3); 7.36–7.38 (m, 2 H, CH of Ar); 7.45 (dd, ^3J = 6.4, ^4J = 3.2, 1 H, CH of Ar); 7.63 (d, ^3J = 7.6, 1 H, CH^6 of pyrroloisoquinoline); 7.74 (td, ^3J = 8.0, ^4J = 1.2, 1 H, CH of Ar); 7.78 (td, ^3J = 7.2, ^4J = 1.2, 1 H, CH of Ar); 8.01 (dd, ^3J = 7.2 Hz, ^4J = 1.6, 1 H, CH of Ar); 8.44 (s, 1 H, CH^4 of coumarin), 8.87 (d, ^3J = 7.6, 1 H, CH of Ar), 9.22 (d, ^3J = 7.6, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 13.2; 13.7; 56.2; 61.4; 61.8; 109.5; 116.1; 116.6; 118.3; 120.7; 121.7; 123.1; 124.0; 125.1; 125.5; 126.5; 127.6; 128.5; 128.7; 129.8; 130.6; 132.4; 143.1; 144.7; 146.4; 157.0; 164.1 (2 CO_2); 180.3. MS (EI, 70 eV): 513 (M^+, 39), 485 (25), 441 (18), 396 (8), 311 (14), 238 (31), 220 (23), 203 (74), 164 (32), 129 (100), 102 (36), 76 (19). Anal.

calc. for $C_{29}H_{23}NO_8$ (513.50): C 67.83, H 4.51, N 2.73; Found: C 67.91, H 4.45, N 2.68.

Di(tert-*butyl) 3-[(8-methoxy-2-oxo-2*H-*chromen-3-yl)carbonyl]pyrrolo [2,1-*a*]*isoquinoline-1,2-dicarboxylate* (Table 2, entry f)

Yield: 518 mg (91 %). Pale yellow powder. M.p. 219–223 °C. (KBr, cm^{-1}): 1,155 and 1,209 1271 (C–O), 1,470 and 1,622 (Ar), 1,713 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.17 (s, 9 H, $OCMe_3$); 1.61 (s, 9 H, $OCMe_3$); 3.95 (s, 1 H, OCH_3); 7.34–7.39 (m, 2 H, CH of Ar); 7.44 (dd, $^3J = 7.6$, $^4J = 2.0$, 1 H, CH of Ar); 7.50 (d, $J = 7.6$, 1 H, CH^6 of pyrroloisoquinoline); 7.72–7.75 (m, 2 H, CH of Ar); 7.95–7.97 (m, 1 H, CH of Ar); 8.46 (dd, $J = 6.2$, $^4J = 3.4$, 1 H, CH of Ar); 8.50 (s, 1 H, CH^4 of coumarin); 8.96 (d, $J = 7.6$, 1 H, CH^5 of isoquinolone). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 27.0; 27.7; 56.2; 82.4; 82.6; 112.2;115.8; 116.3; 118.7; 121.0; 121.8; 123.2; 123.9; 124.2; 125.1; 126.8; 127.3; 127.7; 128.3; 129.24 (C^{6a} of pyrroloisoquinoline and CH of Ar), 130.1; 143.3; 146.0; 146.4; 156.7; 162.6; 164.1; 180.6. MS (EI, 70 eV): 569 (M^+, 10), 513 (5), 485 (21), 457 (45), 413 (8), 368 (9), 238 (14), 211 (64), 194 (19), 178 (19), 139 (17), 56 (100). Anal. calc. for $C_{33}H_{31}NO_8$ (569.61): C 69.59, H 5.49, N 2.46; Found: C 69.63, H 5.60, N 2.39.

*Dimethyl 3-(3-oxo-3*H-*benzo[f]chromen-2-ylcarbonyl)pyrrolo [2,1-*a*]*isoquinoline-1,2-dicarboxylate* (Table 2, entry g)

Yield: 344 mg (68 %). Dirty yellow powder. M.p. 199–205 °C. (KBr, cm^{-1}): 1,210 (C–O), 1,465, 1,524, and 1,642 (Ar), 1,734 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.12 (s, 3 H, OMe); 3.83 (s, 3 H, OMe); 7.65–7.70 (m, 3 H, CH of Ar); 7.74–7.82 (m, 3 H, CH of Ar); 8.03 (dd, $^3J = 8.2$, $^4J = 0.9$, 1 H, CH of Ar); 8.12 (d, $^3J = 8.0$, 1 H, CH of Ar); 8.36 (d, $^3J = 8.8$, 1 H, CH of Ar); 8.49 (d, $J = 8.4$, 1 H, CH of Ar); 8.96 (d, $J = 8.0$, 1 H, CH of Ar); 9.30 (s, 1 H, CH^1 of coumarin); 9.32 (d, $J = 7.2$, 1 H, CH^5 of pyrroloisoquinoline). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 52.2; 52.5; 112.0; 116.6; 116.7; 117.5; 122.0; 122.2; 123.1; 124.1; 125.0; 125.7; 126.5; 127.6; 128.5; 128.9; 129.0; 129.1; 129.9; 129.9; 130.0; 130.2; 132.8; 135.5; 140.8; 154.3; 157.2; 164.4; 164.8; 180.4. MS (EI, 70 eV): 505 (M^+, 30), 474 (8), 310 (9), 283 (79), 252 (100), 238 (13), 223 (34), 193 (28), 165 (26), 139 (76), 115 (15), 102 (13), 63 (14). Anal. calc. for $C_{30}H_{19}NO_7$ (505.48): C 71.28, H 3.79, N 2.77; Found: C 71.03, H 3.95, N 2.91.

*Diethyl 3-(3-oxo-3*H-*benzo[f]chromen-2-ylcarbonyl)pyrrolo [2,1-*a*]*isoquinoline-1,2-dicarboxylate* (Table 2, entry h)

Yield: 384 mg (72 %). Beige powder. M.p. 208 °C (decomp). (KBr, cm^{-1}): 1,204 (C–O), 1,466, 1,565, and 1,627 (Ar), 1,726 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 0.74 (t, $J = 7.2$, 3 H, OCH_2CH_3); 1.23 (t, $J = 7.2$, 3 H, OCH_2CH_3); 3.51 (q, $J = 7.2$, 2 H, OCH_2CH_3); 4.31 (q, $J = 7.0$, 2 H, OCH_2CH_3); 7.65–7.70 (m, 3 H, CH of Ar); 7.73–7.81 (m, 3 H, CH of Ar); 8.02 (dd, $^3J = 8.2$,

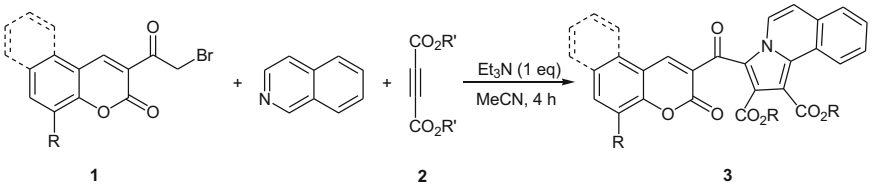
^4J = 0.9, 1 H, CH of Ar); 8.12 (d, J = 8.0, 1 H, CH of Ar); 8.35 (d, J = 9.2, 1 H, CH^6 of pyrroloisoquinoline); 8.50 (d, J = 8.4, 1 H, CH of Ar); 8.96 (d, J = 8.0, 1 H, CH of Ar); 9.30 (s, 1 H, CH^1 of coumarin); 9.31 (d, J = 8.8, 1H, CH of Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 12.9; 13.7; 61.4; 61.8; 109.3; 112.0; 116.6 (2 CH of Ar); 122.0; 122.4; 123.2; 124.1; 125.1; 125.7; 126.5; 127.6; 128.4; 128.8; 129.0; 129.2; 129.4; 129.8; 129.88; 129.94; 132.7; 135.5; 140.9; 154.3; 157.1; 164.1; 164.4; 180.5. MS (EI, 70 eV): 533 (M^+, 14), 505 (10), 311 (53), 283 (7), 266 (26), 238 (72), 223 (30), 194 (45), 167 (69), 139 (100), 115 (24). Anal. calc. for $C_{32}H_{23}NO_7$ (533.53): C 72.04, H 4.34, N 2.63; Found: C 71.93, H 4.49, N 2.69.

*Di(*tert*-butyl) 3-(3-oxo-3*H*-benzo[f]chromen-2-ylcarbonyl)pyrrolo [2,1-*a*]isoquinoline-1,2-dicarboxylate* (Table 2, entry i)

Yield: 454 mg (77 %). Yellow powder. M.p. 225 °C (decomp). (KBr, cm^{-1}): 1,154 and 1,211 (C–O), 1,554, and 1,624 (Ar), 1,723 (br., 4 C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.05 (s, 9 H, OCMe$_3$); 1.61 (s, 9 H, OCMe$_3$); 7.54 (d, J = 7.6, 1 H, CH of Ar); 7.67 (t, J = 7.0, 1 H, CH of Ar); 7.68 (d, J = 8.0, 1 H, CH of Ar); 7.74–7.78 (m, 3 H, CH of Ar); 7.97–7.99 (s, 1 H, CH of Ar); 8.11 (d, J = 7.6, 1 H, CH of Ar); 8.35 (d, J = 9.2, 1 H, CH of Ar); 8.50–8.54 (m, 2 H, CH of Ar); 9.05 (d, ^3J = 7.6, ^4J = 2.0, 1 H, CH^5 of isoquinolone); 9.31 (s, 1 H, CH^1 of coumarin). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 26.9; 27.7; 82.4; 82.5; 112.1; 112.5; 115.7; 116.5; 122.1; 122.4; 123.2; 124.0; 124.4; 125.7; 126.5; 127.7; 127.9; 128.2; 128.9; 129.1; 129.2; 129.3; 129.4; 129.9; 130.3; 135.8; 141.6; 154.5; 157.1; 162.8; 164.1; 180.8. MS (EI, 70 eV): 589 (M^+, 8), 533 (28), 505 (23), 477 (31), 388 (12), 255 (40), 238 (40), 211 (100), 194 (36), 166 (32), 139 (64), 115 (17), 56 (74). Anal. calc. for $C_{36}H_{31}NO_7$ (589.64): C 73.33, H 5.30, N 2.38; Found: C 73.39, H 5.39, N 2.48.

Results and discussion

Accordingly, and in continuation of our studies on the synthesis of new polycyclic heterocyclic compounds [43–49], and coumarin moiety, we were encouraged to synthesize functionalized coumarin bearing pyrrolo[2,1-*a*]isoquinoline derivatives by the reaction of 3-(2-bromoacetyl)coumarins **1**, isoquinoline and dialkyl acetylenedicarboxylates **2** in the presence of one equivalent triethylamine (Scheme 3).



Scheme 3 Synthesis of dialkyl 3-[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylates

Initially, we synthesized 3-acetylcoumarin derivatives by the reaction of salicylaldehydes and β-keto esters in the presence of piperidine as a catalyst [44–49]. Then 3-(2-bromoacetyl)coumarins **1** were prepared by reaction of 3-acetylcoumarin with NBS in the presence of *p*-toluenesulfonic acid and the products have been compared to literature [50, 51]. Then, the 3-bromoacetylcoumarin (**1a**), isoquinoline and dimethyl acetylenedicarboxylate (**2a**) were selected as the model substrates and the effect of solvents and bases has been studied to optimize the reaction conditions. The best results were obtained by performing the model reaction in MeCN in the presence of one equivalent triethylamine (see Table 1).

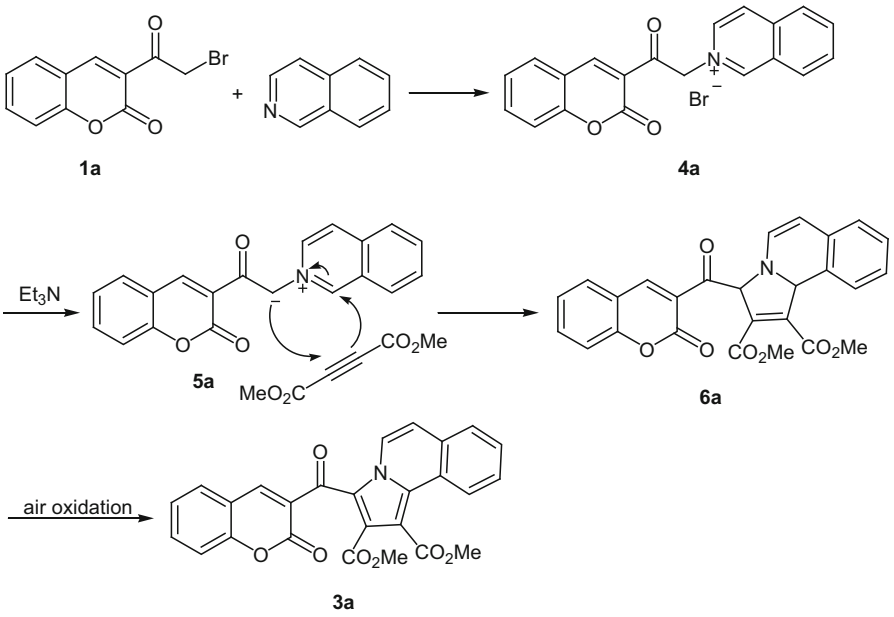
When we used DMF as a solvent, the same results were obtained (TLC) but the yield of isolated product decreased due to its higher solubility in DMF in comparison with MeCN and thus we used acetonitrile in this reaction to gain higher isolated yields. When we used inorganic bases such as K_2CO_3 and NaOH, complex mixture has been obtained (Table 1, entry 2, 3). After establishing optimal conditions, we explored the scope of the reaction leading to product **3**.

For this purpose, we extended this promising reaction by using various 3-(2-bromoacetyl)coumarin **1** and dialkyl acetylenedicarboxylates **2**. The reactions are generally clean and the desired products **3a–i** were obtained in good yields.

To extend our knowledge of this transformation, we performed the same reactions with various alkyl propiolates, but these reactions failed and a complex mixture was obtained. The alkyl propiolates are unsymmetrical acetylene derivatives, and there are two regioisomeric cycloaddition possible on the triple bond. They are also highly active molecules in comparison with dialkyl acetylenedicarboxylate leading to complex mixtures in this transformation. The structures of compounds **3a–i** were deduced from their elemental analysis, IR, and high-field ^{1}H- and ^{13}C-NMR spectra. The mass spectrum of **3a** displayed the molecular ion peak at *m/z* 455, which is in agreement with the proposed structure. The IR spectrum of this compound showed a broad absorption band due to the four C=O stretching frequency at 1,735 cm^{-1}, and absorption bands at 1,625, 1,508, 1,455, and 1,203 cm^{-1} are assigned to the C=C and C–O groups.

The ^{1}H NMR spectrum of **3a** showed five *doublet* signals [δ 7.53, ($J = 8.4$), 7.63, ($J = 7.6$), 8.00, ($J = 7.2$), 8.87, ($J = 8.0$), and 9.24, ($J = 7.2$)], one *triplet* signal (δ 7.45, ($J = 7.4$)), one doublet of doublet signals [δ 7.82, ($J = 8.0$ and $J = 1.2$)] and one *multiplet* signal (δ 7.72–7.80) for aromatic H-atoms and also three sharp *singlet* signals (δ 3.32, 3.87 and 8.46) for two OMe groups and CH of the chromene ring, respectively. The ^{13}C NMR spectrum of **3a** exhibits 26 distinct signals in agreement with the suggested structure.

According to these results, a plausible mechanism for the three-component reaction is proposed (Scheme 4). At first, nucleophilic attack of isoquinoline to 3-(2-bromoacetyl)coumarin (**1a**) leads to isoquinolinium salt **4a**. Next, the *N*-ylide **5a** was obtained by deprotonation of **4a** with triethylamine. Then, 1,3-cycloaddition on to the triple bond leads to intermediate **6a**, and finally air oxidation of **6a** yields the desired product **3a**.



Scheme 4 A plausible mechanism for the formation of products **3a–i**

Conclusions

In summary, we have presented the synthesis of new coumarin derivatives 3 by a three-component reaction. Easy performance, good yields, and easy purification are the main aspects of the present method. The products described in this article have two important biological active moieties, coumarin and pyrrolo[2,1-*a*]isoquinoline. To our knowledge, this is the first report on this class of coumarins and there are no other efficient methods for their synthesis. Due to the importance of these two scaffolds, synthetic and biological applications of compounds 3 can be considered in the near future.

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