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A FACILE SYNTHESIS OF ISOCOUMARINO[3',4':4,5]PYRROLO[3,2-*c*]-COUMARINS FROM 4-AMINOCOUMARINS AND NINHYDRIN

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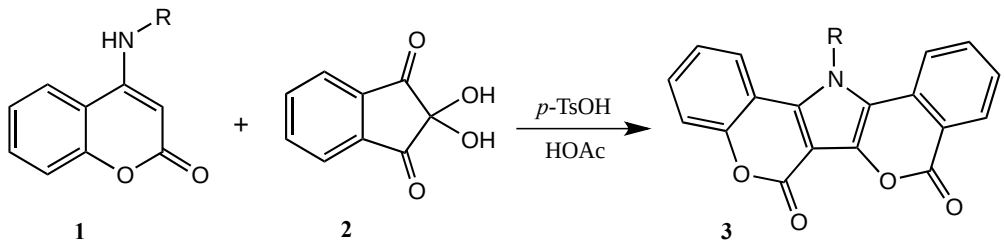
Abstract – An efficient method for the synthesis of novel isocoumarino-[3',4':4,5]pyrrolo[3,2-*c*]coumarins was described. The construction of this new fused heterocycles system was achieved undergo a domino reaction of 4-amino-coumarins with ninhydrin in good yields.

Coumarins and isocoumarins are an important class of naturally occurring lactones,[1] which have attracted the attention of chemists because of their various biological activities such as antioxidative,[2] anticancer[3] antiviral[4] and antifungal activities.[5] The development of a new and efficient methodology for the synthesis of biologically potent coumarins/isocoumarins and their carbo/hetero annulated analogues has drawn great attention of synthetic as well as medicinal chemists.[1,6] Particularly pyrrolocoumarin derivatives, have been the subject of continued interest in recent years.[7]

On the other hand, although a number of synthetic methods have been developed for the construction of pyrrole-fused coumarins/isocoumarins,[8] not a single report has been given on the synthesis of isocoumarinopyrrole-fused coumarins with the help of green methodology, so far.

Recently, we have developed several domino reactions toward the construction of diverse heterocyclic structures.[9] In continuation of this project, we now report the novel isocoumarino[3',4':4,5]pyrrolo-[3,2-*c*]coumarins **3** preparation *via* domino reaction from 4-aminocoumarins[10] **1** with ninhydrin **2** in the presence *p*-toluenesulfonic acid (*p*-TsOH) (Scheme 1).



1 **2** **3**

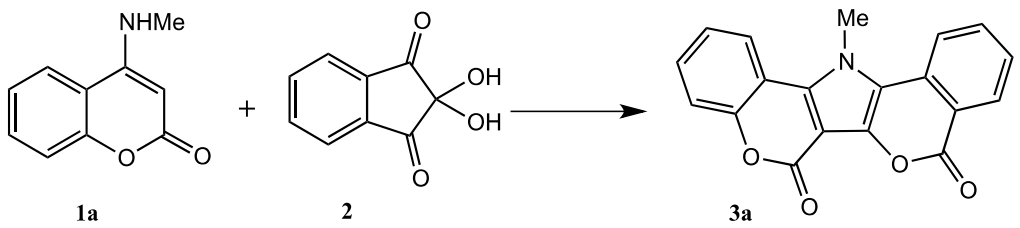
Scheme 1. Synthesis of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins

Microwave technology has been demonstrated to speed up reactions, often achieving good purity and product yield.[11] We decided to investigate the selectivity of the reaction between amino-substituted coumarins at C4 (**1**) and ninhydrin (**2**) and explore the effect of microwave irradiation, which in many cases has been reported to increase the selectivity of chemical reactions.[12]

In our initial study, the domino reaction of *N*-methyl 4-aminocoumarin (**1a**) with ninhydrin (**2**) was carried out in DMF at 100 °C for 20 min under MW, and the expected *N*-methylisocoumarino[3',4':4,5]-pyrrolo[3,2-*c*]coumarin **3a** was not observed at all (Table 1, entry 1). The desired product **3a** was provided in 42% yield when HOAc was used as an acidic media at 100 °C under MW (entry 2). Gratifyingly, this reaction worked more efficiently in HOAc using 1.0 equiv of *p*-TsOH as a promoter, affording the corresponding product **3a** in 62% yield (entry 3). The best outcome was observed in HOAc using 1.5 equiv of *p*-TsOH (entries 3-6). The influence of reaction temperature was also optimized, only reaction temperature of 100 °C was found to facilitate the reaction, delivering a higher yield (75%) (entry 4). Further increase (110 °C) or decrease (90 °C) of reaction temperature did not push this domino reaction forward (entries 7 and 8). Subsequently, the reaction was also tested at different power (entries 9 and 10) and the best result was obtained at 200 W.

On the other hand, in order to monitor the progress of the reaction, a mixture of **1a** and **2** was in HOAc under conventional heating (instead of microwave irradiation) using 1.5 equiv of *p*-TsOH. The desired product **3a** was observed after 30 min and it increased gradually, and reached to maximum at 180 min with the completion of the reaction on TLC (entry 11).

In addition, other organic acids such as sulfamic acid (SA), trifluoroacetic acid (TFA), and trifluoromethanesulfonic acid (TfOH) were also tested under MW, the yield of the product **3a** was 55% to 68% and 64% respectively (entries 12-14). The title compound **3a** was characterized by IR, NMR spectroscopy. IR spectrum of **3a** showed peaks at 1670, 1651 cm^{-1} due to carbonyl group. ^{1}H NMR spectrum of compound **3a** showed eight aromatic protons were observed in the range of δ 7.42-8.39. The singlet of the three protons for *N*-methyl groups at δ 4.61. Moreover, the ^{13}C NMR spectrum agreed with the proposed structure **3a**. The carbonyl group resonances in ^{13}C NMR spectra of **3a** appear at 160.1 and 163.9 ppm.



Scheme 2. Synthesis of *N*-methylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin

Table 1. Optimization of reaction conditions on the synthesis of **3a**

Entry	Catalyst / (mol%)	Reaction Conditions	Temp (°C)	Time (min)	Yield (%)
1	none	MW / DMF at 200W	100	20	Trace
2	none	MW / HOAc at 200W	100	20	42
3	*p*-TsOH (100)	MW / HOAc at 200W	100	20	62
4	*p*-TsOH (150)	MW / HOAc at 200W	100	20	75
5	*p*-TsOH (50)	MW / HOAc at 200W	100	30	51
6	*p*-TsOH (200)	MW / HOAc at 200W	100	20	72
7	*p*-TsOH (150)	MW / HOAc at 200W	110	20	73
8	*p*-TsOH (150)	MW / HOAc at 200W	90	20	70
9	*p*-TsOH (150)	MW / HOAc at 250W	100	20	64
10	*p*-TsOH (150)	MW / HOAc at 150W	100	20	48
11	*p*-TsOH (150)	HOAc / reflux	120	180	62
12	SA (150)	MW / HOAc at 200W	100	20	55
13	TFA (150)	MW / HOAc at 200W	100	20	68
14	TfOH (150)	MW / HOAc at 200W	100	20	64

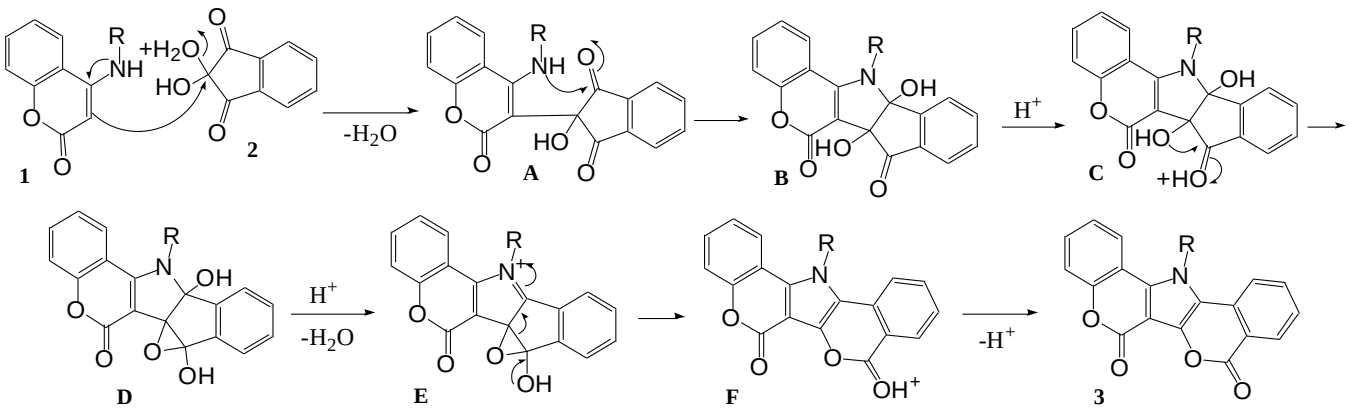
Under these optimized reaction conditions, a series of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins **3** were synthesized. As shown in Table 2, the reaction was successful for *N*-substituted 4-aminocoumarins **1** incorporating alkyl (entries 1-5) as well as aromatic (entries 6-8) R groups substituents reacted efficiently giving good yields (73-82%).

Table 2. Synthesis of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins **3**

			Classical method		MW method	
Entry	Product		Time (h)	Yield (%)	Time (min)	Yield (%)
1	**3a**	Me	3	62	20	75
2	**3b**	Et	3	60	20	73
3	**3c**	*n*-Pr	3	65	20	81
4	**3d**	*n*-Hex	4	60	25	76
5	**3e**	Bn	3	70	15	82
6	**3f**	Ph	4	67	25	79
7	**3g**	4-FC_6H_4	4	64	30	75
8	**3h**	4-ClC_6H_4	4	65	30	76

The structure of the product **3** was confirmed by IR, NMR spectroscopy and elemental analysis. The present work represents the special example for construction of these types of pentacyclic system heterocycles containing coumarin, isocoumarin and pyrrole unit with high regioselectivity.

On the basis of literature reports[8a,8d] and observations of the above results, the proposed mechanism of the process is summarized in Scheme 2. Firstly, amine **1** reacts with protonated **2** to generate intermediate B. The intermediate B undergoes two subsequent intramolecular cyclizations to give three-membered-ring intermediate D; ring-opening and deprotonation follow, to yield the final isocoumarinopyrrole-fused coumarins **3**.



Scheme 3. Proposed mechanism for the synthesis of compounds **3**

In summary, we have developed a convenient and efficient methodology for synthesizing a diverse range of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins through a novel domino reaction from 4-amino-coumarins with ninhydrin under microwave irradiation as well as conventional method. Features of this strategy include the relatively mild conditions, convenient one-pot operation, easy work-up, inexpensive reagents and good yields.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H and N analyses were performed by a HP-MOD 1106 microanalyzer. The preparation of 4-aminocoumarins (**1**)[10] were according to the literature procedure. All other chemicals used in this study were commercially available.

Typical procedure for the preparation of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins under microwave irradiation (Method A): To a solution of 4-aminocoumarins **1** (1.0 mmol) and ninhydrin **2** (1.0 mmol) in HOAc (10.0 mL), *p*-TsOH (260 mg, 1.5 mmol) was added, and the reaction at 100 °C under

microwave irradiation (200 W). After completion monitored by TLC, the reaction mixture was then cooled to room temperature and then diluted with cold water (20 mL). The solid was filtered and recrystallized from HOAc to to afford the corresponding products **3a-h**.

Typical procedure for the preparation of isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarins under thermal condition (Method B): A mixture of 4-aminocoumarins **1** (1.0 mmol), ninhydrin **2** (1.0 mmol) and *p*-TsOH (260 mg, 1.5 mmol) was refluxed in HOAc (15.0 mL) for the given time (Table 2) (monitored by TLC). At the end of the reaction, the reaction mixture was cooled to rt, and the water (30 mL) was added to the mixture. The solid was filtered and recrystallized from HOAc to afford the corresponding products **3a-h**.

***N*-Methylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3a):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1670, 1651 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO-d_6): δ 4.61 (3H, s, CH_3), 7.42 (1H, d, J = 8.0 Hz), 7.55-7.62 (3H, m), 8.02-8.03 (1H, m), 8.21 (1H, d, J = 8.0 Hz), 8.26 (1H, d, J = 7.6 Hz), 8.39 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.0, 96.4, 112.2, 117.4, 118.4, 119.8, 122.3, 125.8, 128.1, 128.5, 129.2, 130.1, 130.9, 132.2, 136.7, 137.2, 151.3, 160.1, 163.9. *Anal*. Calcd for $C_{19}H_{11}NO_4$: C 71.92, H 3.49, N 4.41. Found: C 71.98, H 3.51, N 4.45.

***N*-Ethylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3b):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1678, 1654 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO-d_6): δ 1.93 (3H, t, J = 7.2 Hz, CH_3), 5.04 (2H, q, J = 7.2 Hz, CH_2), 7.38 (1H, d, J = 7.6 Hz), 7.55-7.60 (3H, m), 7.99-8.03 (1H, m), 8.13 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 7.6 Hz), 8.34 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 43.6, 109.9, 117.9, 118.9, 119.5, 121.8, 125.7, 126.1, 128.2, 129.4, 129.5, 131.0, 132.8, 135.9, 136.9, 137.9, 151.7, 160.5, 161.2. *Anal*. Calcd for $C_{20}H_{13}NO_4$: C 72.50, H 3.95, N 4.23. Found: C 72.58, H 3.98, N 4.24.

***N*-*n*-Propylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3c):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1660, 1652 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO-d_6): δ 1.33 (3H, t, J = 7.2 Hz, CH_3), 2.37-2.39 (2H, m, CH_2), 4.93-4.94 (2H, m, CH_2), 7.55-7.66 (4H, m), 8.07-8.16 (3H, m), 8.51 (1H, d, J = 7.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.1, 22.6, 49.8, 112.3, 117.5, 117.7, 118.6, 119.4, 121.8, 126.0, 126.2, 128.1, 129.4, 129.5, 130.9, 132.5, 136.1, 136.9, 151.5, 160.7, 164.2. *Anal*. Calcd for $C_{27}H_{17}NO_4$: C 77.32, H 4.09, N 3.34. Found: C 77.39, H 4.13, N 3.37.

***N*-*n*-Hexylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3d):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1679, 1652 cm^{-1} (C=O); ^1H NMR (400 MHz, DMSO-d_6): δ 0.98 (3H, t, J = 7.2 Hz, CH_3), 1.42-1.57 (4H, m), 1.76 (2H, m, CH_2), 2.30-2.41 (2H, m), 4.95 (2H, m, CH_2), 7.50-7.75 (4H, m), 8.02-8.16 (3H, m), 8.47 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.5, 21.9, 25.6, 29.2, 30.8, 48.6, 98.34, 112.7, 117.4, 117.5, 118.5, 119.5, 121.8, 126.0, 128.1, 129.2, 130.8, 132.4, 135.8, 136.9, 137.5, 151.4, 160.3, 164.0. *Anal*. Calcd for $C_{24}H_{21}NO_4$: C 74.40, H 5.46, N 3.62. Found: C 74.48, H 5.49, N 3.66.

***N*-Benzylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3e):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1669, 1652 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.22 (2H, s, CH_2), 7.28 (1H, t, J = 6.8 Hz), 7.37-7.39 (3H, m), 7.43-7.47 (2H, m), 7.53-7.58 (3H, m), 7.71 (1H, d, J = 8.0 Hz), 7.77-7.79 (2H, m), 8.31 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.2, 98.2, 113.1, 117.4, 118.3, 119.0, 120.5, 122.8, 125.2, 126.3, 128.0, 128.4, 129.4, 129.8, 130.6, 132.2, 135.4, 135.5, 136.1, 139.1, 152.4, 155.4, 161.0. *Anal*. Calcd for $C_{25}H_{15}NO_4$: C 76.33, H 3.84, N 3.56. Found: C 76.39, H 3.87, N 3.59.

***N*-Phenylisocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3f):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1673, 1653 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.59 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz), 7.03 (1H, t, J = 7.6 Hz), 7.44-7.52 (4H, m), 7.67-7.69 (2H, m), 7.77-7.88 (3H, m), 8.33 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 96.9, 113.2, 117.6, 118.0, 118.3, 118.9, 119.4, 121.8, 125.3, 126.4, 128.0, 128.1, 130.9, 131.1, 131.7, 131.9, 136.2, 139.5, 151.7, 152.3, 161.1, 164.6. *Anal*. Calcd for $C_{24}H_{13}NO_4$: C 75.98, H 3.45, N 3.69. Found: C 76.05, H 3.48, N 3.73.

***N*-(4-Fluorophenyl)isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3g):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1669, 1656 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.73 (1H, d, J = 8.0 Hz), 6.88 (1H, d, J = 8.0 Hz), 7.15-7.19 (1H, m), 7.59-7.64 (5H, m), 7.80-7.83 (3H, m), 8.53 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 98.5, 113.5, 117.4, 118.3, 118.5, 118.9, 120.1, 121.4, 125.8, 126.3, 128.0, 128.6, 130.5, 131.3, 131.9, 132.2, 132.6, 137.2, 151.2, 152.4, 161.3, 164.4. *Anal*. Calcd for $C_{24}H_{12}FNO_4$: C 72.54, H 3.04, N 3.52. Found: C 72.59, H 3.05, N 3.55.

***N*-(4-Chlorophenyl)isocoumarino[3',4':4,5]pyrrolo[3,2-*c*]coumarin (3h):** Yellow crystals. mp > 300 °C; IR (KBr): *v* 1667, 1654 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.71 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 8.0 Hz), 7.19-7.21 (1H, m), 7.57-7.67 (6H, m), 7.77-7.79 (2H, m), 8.51 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 97.4, 113.6, 117.4, 118.4, 118.5, 118.8, 119.2, 121.6, 125.5, 126.2, 128.0, 128.3, 130.5, 131.2, 131.8, 132.0, 132.4, 136.3, 151.8, 152.4, 161.0, 164.9. *Anal*. Calcd for $C_{24}H_{12}ClNO_4$: C 69.66, H 2.92, N 3.38. Found: C 69.72, H 2.95, N 3.41.

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