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Graphical abstract

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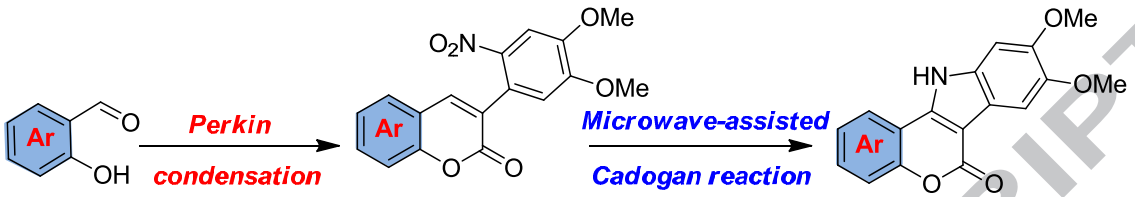

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A convenient approach to the design and synthesis of indolo[3,2-*c*]coumarins via the microwave-assisted Cadogan reaction

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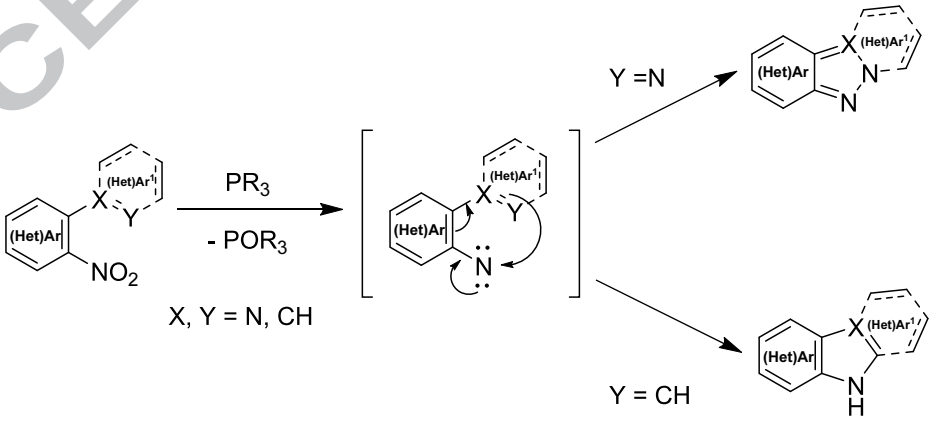
A B S T R A C T

3-(4,5-Dimethoxy-2-nitrophenyl)coumarins bearing various substituents on the benzene ring of the coumarin system have been prepared from salicylaldehydes and 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile by means of the Perkin condensation. Further cyclization of these 3-aryl coumarins through the microwave-assisted Cadogan reaction afforded the corresponding indolo[3,2-*c*]coumarins in good to excellent yields.

Keywords: Indolo[3,2-*c*]coumarins, 3-Aryl coumarins, Salicylaldehydes, Cadogan reaction, Microwave-assisted synthesis, Reductive cyclization

The deoxygenation of *C*-nitroso- or *C*-nitro-substituted (hetero)arenes by the action of trivalent phosphorus-containing compounds (e.g. triethyl phosphite and triphenylphosphine) occurs via the Cadogan reaction.[1] When conducted in an intramolecular sense, N-containing heterocycles are formed. It has been assumed that the transformation takes place through a nitrene-type intermediate (Scheme 1).[2] The Cadogan reaction is a simple and convenient synthetic route to indoles, carbazoles, and other condensed derivatives of pyrroles, imidazoles, pyrazoles and triazoles.[3]



Scheme 1. The formal mechanism for the Cadogan reaction

This reaction has been improved by using microwave irradiation instead of conventional reflux for several hours. This has led to reduced reaction times of two minutes at best, and increased yields of the major products.[4] Although a number of aromatic and heteroaromatic nitro compounds have been used successfully in the Cadogan cyclization, there are no reports in the literature on using coumarin derivatives in this reaction.

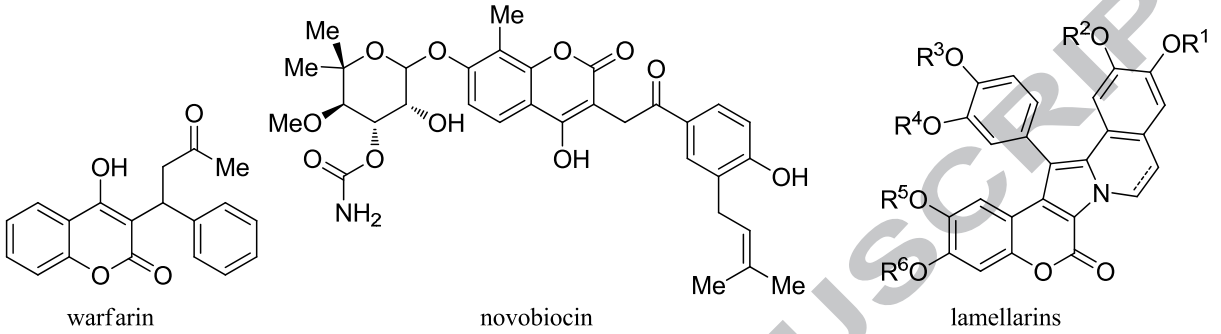


Figure 1. Bioactive coumarins

Coumarins represent an important family of oxygen-containing fused heterocycles, which are widely distributed in Nature, especially in plants. Natural coumarins and their synthetic analogs exhibit a wide range of physiological activities, such as anti-oxidant,[5a] antifungal,[5b] antihelmintic,[5c] anticoagulant (warfarin),[5d] antibacterial (novobiocin)[5e] and antiviral[5f] properties, including anti-HIV[5g] (lamellarines) and anti-HCV[5h] activities (Figure 1). Also, coumarin derivatives are important as fluorescent indicators, optical brighteners and photosensitizers or dyes for lasers and DSSC (dye-sensitized solar cell).[6,7] The development of novel synthetic approaches to coumarin derivatives is of significant synthetic importance.

Indolo[3,2-*c*]coumarins [chromeno[4,3-*b*]indol-6(11*H*)-ones] are nitrogen-containing analogs of naturally occurring compounds known as coumestans (benzofuro[3,2-*c*]chromen-6-one), examples of which include coumestrol, wedelolactone and plicadin, which are found in various plants (Figure 2).

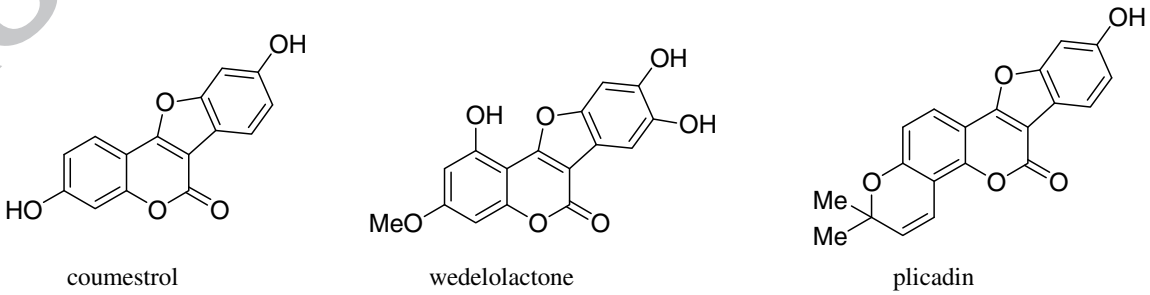
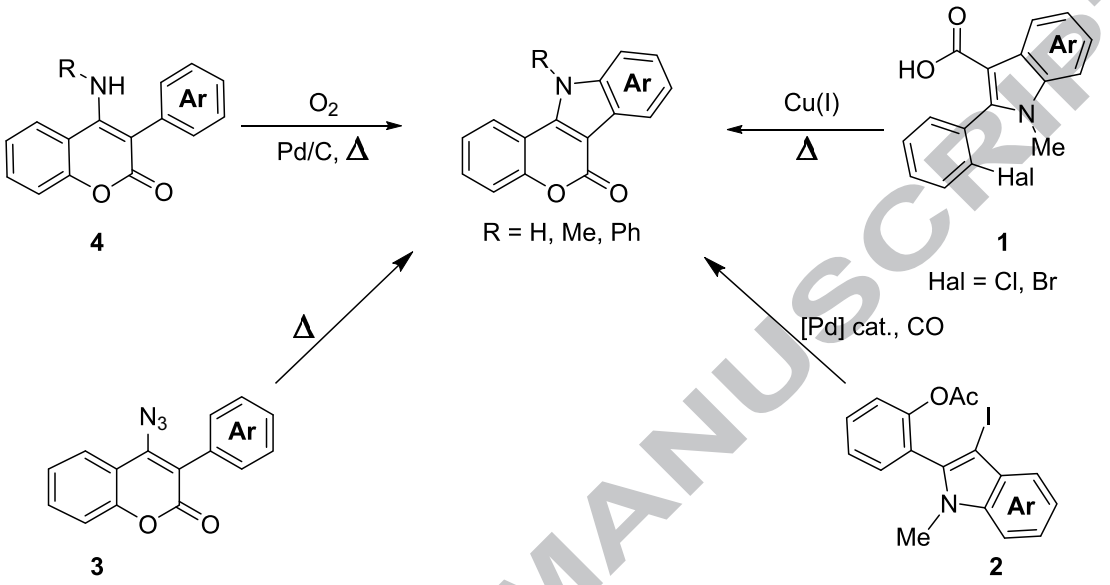


Figure 2. Naturally occurring coumestans

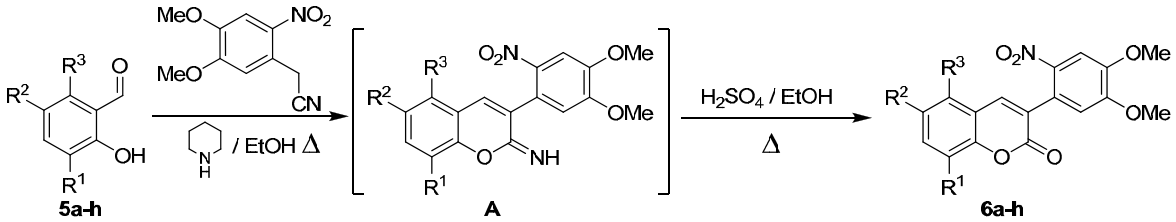
Since many coumestans possess estrogenic,[8a] antitumor[8b] and antihepatotoxic[8c] activities, the development of synthetic approaches to new derivatives and close structural analogues of coumestans, as well as elucidation of their pharmacological properties are worthwhile.

In this paper, we report a novel and convenient synthetic approach to indolo[3,2-*c*]coumarins based on the microwave-assisted Cadogan cyclization of 3-(2-nitroaryl)-substituted coumarins.



Scheme 2. Synthetic routes to indolo[3,2-*c*]coumarins

It should be noted that a number of synthetic routes to indolo[3,2-*c*]coumarins have been described in the literature, including copper-catalyzed cyclization of 2-(2-halophenyl)indole-3-carboxylic acids **1**,[9a] palladium-catalyzed carbonylation/lactonization of 2-(2-acetoxyphenyl)-3-iodoindoles **2**,[9b] thermal cyclization of 4-azido-3-arylcoumarins **3**,[9c] and dehydrogenation of 4-amino-3-arylcoumarins **4**[9d] (Scheme 2). These methods utilize derivatives of coumarin and indole, which have to be prepared in several steps. In contrast, our approach to the synthesis of indolo[3,2-*c*]coumarins can be realized in two steps from commercially available reagents. As a result of the Perkin condensation of salicylaldehydes **5a-h** with 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile, a number of 3-(4,5-dimethoxy-2-nitrophenyl)coumarins **6a-h** have been obtained.[10] This transformation was carried out in ethanol in the presence of piperidine as the catalyst, and the intermediate imines **A** were hydrolyzed with sulfuric acid without isolation (see Scheme 3, Table 1). Coumarins **6a-g** were obtained in 83–98% yields and required no further purification after filtration (purity assessed by ^{1}H NMR). An exception was coumarin **6h** for which crystallization from DMF was necessary to obtain the target product, albeit in a relatively low yield of 27%.



Scheme 3. Synthesis of coumarins **6a-h**

Table 1. Yields and melting points of coumarins **6**

Salicylaldehyde	R^1	R^2	R^3	Coumarin	Yield (%)	Mp (°C)
5a	H	H	H	**6a**	98	232 – 233
5b	OMe	H	H	**6b**	94	236 – 237
5c	OMe	Br	H	**6c**	92	254 – 255
5d	H	OMe	H	**6d**	87	232 – 234
5e	Br	Br	H	**6e**	83	237 – 238
5f	H	Cl	H	**6f**	85	274 – 275
5g	H	Br	H	**6g**	95	278 – 280
5h	H	Benzo[*f*]		**6h**	27	282 – 284

The starting 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile required for the Perkin condensation was prepared by nitration of homoveratronitrile with nitric acid in glacial acetic acid.[11] Attempts to synthesize coumarins **6** by means of the Perkin condensation of salicylaldehydes with ethyl 2-(4,5-dimethoxy-2-nitrophenyl)acetate in the presence of piperidine as the catalyst failed, even with a stronger base, such as potassium *tert*-butoxide. The structures of coumarins **6** were confirmed by elemental analysis and ^{1}H, ^{13}C NMR and IR spectroscopy. However, the ^{13}C NMR spectra of coumarins **6f,g** could not be obtained due to the poor solubility of these compounds in deuterated solvents. The structures of coumarins **6** were established unequivocally by X-ray crystallographic analysis, performed on compound **6a** (Figure 3).[12]

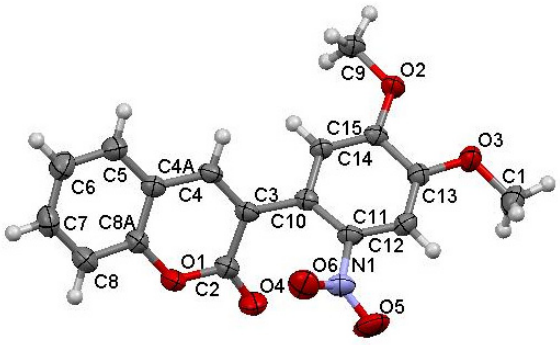
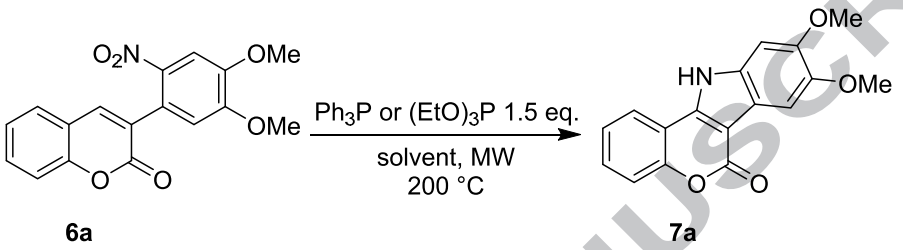


Figure 3. Mercury[13] representation of the X-ray crystal structure of **6a.**

Thermal ellipsoids at 50% probability.

The second step in the synthesis of indolo[3,2-*c*]coumarins was reductive cyclization of compounds **6**. We decided to study the microwave-assisted Cadogan reaction for the synthesis of indolo[3,2-*c*]coumarins **7**, as it was reported earlier that the use of the microwave-assisted technique was effective for various substrates.[4b] The results obtained demonstrate that the microwave-assisted Cadogan reaction was successful for the preparation of compounds **7**. Optimization of the temperature, time, and solvents was performed on the synthesis of coumarin **7a**. Triphenylphosphine or triethyl phosphite were used as reducing agents in these transformations (see Table 2 and Scheme 4).



6a **7a**

Scheme 4. The Cadogan cyclization of coumarin **6a**

Table 2. Optimization of the conditions for MW-assisted Cadogan cyclization

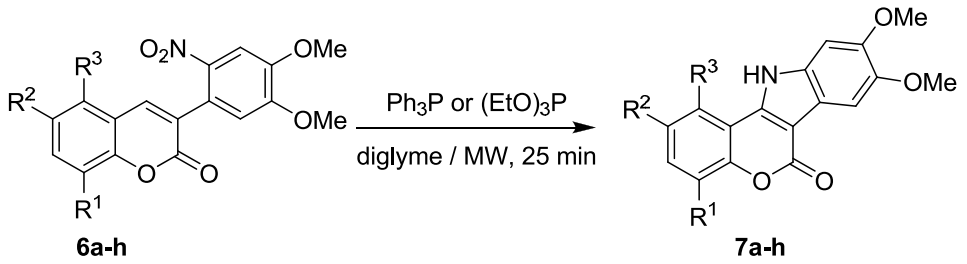
Entry	Solvent	Time (min)	Yield (%) with Ph_3P[a]	Yield (%) with $(EtO)_3P$[a]
1	1,2-dichlorobenzene	5	(**6a**/**7a**)[b]	(**6a**/**7a**)[b]
2	1,2-dichlorobenzene	10	41	67
3	1,2-dichlorobenzene	25	54	61
4	DMF	25	0	0
5	**Diglyme**	**25**	**68**	**71**

[a] 1 mmol of **6a**, 3 mmol of Ph_3P or $(EtO)_3P$ and 2.5 ml of an appropriate solvent were used

[b] A mixture of **6a** and **7a** was obtained with low conversion of the starting material

It was found that indolo[3,2-*c*]coumarin **7a** was formed in the highest yield when the reaction mixture was heated at 200 °C for 25 minutes in diglyme under microwave irradiation (Table 2, entry 5). The yields of **7a** were slightly different when triphenylphosphine or triethyl phosphite were used under the same reaction conditions.

The optimized conditions for the preparation of **7a** were used for the synthesis of other indolo[3,2-*c*]coumarins **7**.[14] However, triphenylphosphine proved to be unsuitable for the syntheses of **7c-e**. Instead, these compounds were obtained in good yields when triethyl phosphite was used as the reducing agent. Indeed, triethyl phosphite proved to be a more effective reagent for cyclization of coumarins **6**. The exception was coumarin **6h**, which did not undergo cyclization in the presence of triethyl phosphite (see Scheme 5 and Table 3).



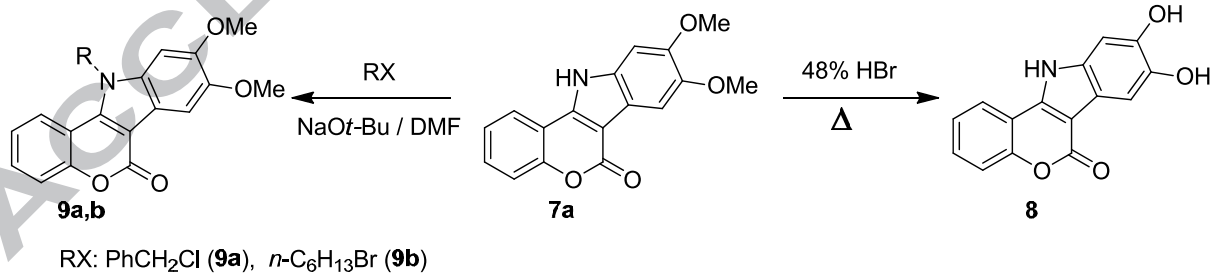
Scheme 5. Synthesis of indolo[3,2-*c*]coumarins **7** via the Cadogan cyclization

Table 3. Yields of indolo[3,2-*c*]coumarins **7** with Ph_3P and $(EtO)_3P$.

Coumarin	R^1	R^2	R^3	Indolo[3,2-*c*]coumarin	Yield (%) with Ph_3P	Yield (%) with $(EtO)_3P$
6a	H	H	H	**7a**	68	71
6b	OMe	H	H	**7b**	68	86
6c	OMe	Br	H	**7c**	0	92
6d	H	OMe	H	**7d**	0	89
6e	Br	Br	H	**7e**	0	73
6f	H	Cl	H	**7f**	61	82
6g	H	Br	H	**7g**	64	83
6h	H	Benzo[*f*]		**7h**	58	0

It should be noted that indolo[3,2-*c*]coumarins **7a-h** were obtained in good to excellent yields and in analytically pure form without the need for further purification. All products **7** had very low solubility in a majority of organic solvents, while their melting points exceeded 350 ˚C.

Two methods for the further modification of indolo[3,2-*c*]coumarin **7a** have been studied. Demethylation of compound **7a** was performed with 48% hydrobromic acid under reflux to give the corresponding dihydroxy derivative **8**. 11-Substituted compounds **9a,b** were isolated in moderate yields via alkylation of indolo[3,2-*c*]coumarin **7a**. This synthesis was carried out in DMF at room temperature in the presence of sodium *tert*-butoxide as the base (Scheme 6).



Scheme 6. Modifications of indolo[3,2-*c*]coumarin **7a**

The structure of benzylated derivative **9a** was confirmed by X-ray crystallography (Figure 4).[15] This analysis provided indirect proof for the structures of indolo[3,2-*c*]coumarins **7**, in addition to the ^1H and ^{13}C NMR spectral data and elemental analyses.

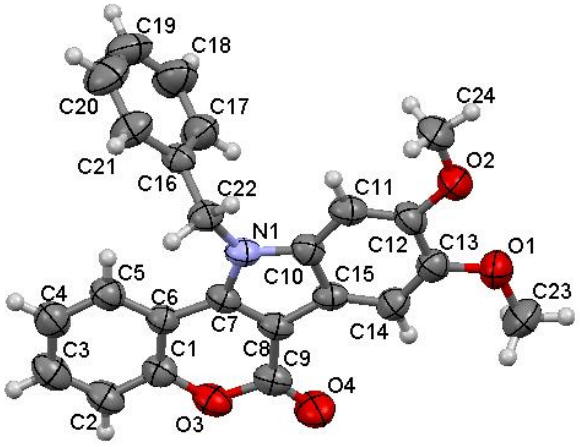


Figure 4. Mercury[13] representation of the X-ray crystal structure of **9a.** Thermal ellipsoids at 50% probability.

In summary, we have developed a convenient and highly efficient two-step synthesis of indolo[3,2-*c*]coumarins from commercially available salicylaldehydes by means of the Perkin condensation, followed by microwave-assisted Cadogan cyclization. Further studies on the use of this approach for the synthesis of other 3-(hetero)arylcoumarins containing a nitro group on the 3-(hetero)aryl substituent are in progress.

Acknowledgments

This work was supported by the Ural Branch of the Russian Academy of Sciences (Grants № 12-P-3-1014, 12-P-3-1030, 12-T-3-1025 and 12-T-3-1031), the State Program for the Supporting of Leading Scientific Schools of the Russian Federation (grant NSh 5505.2012.3), the Russian Foundation for Basic Research (research projects No. 12-03-31574-mol_a, 13-03-96049-r_ural_a), and the Ministry of Education and Science of the Russian Federation (projects № 8430 and 8634).

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10. General procedure for the preparation of coumarins **6**. Piperidine (0.03 ml, 5 mol%) was added to a warm solution of the appropriate salicylaldehyde **5** (5 mmol) and 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile (1.12 g, 5 mmol) in EtOH (10 ml). The resulting solution was refluxed with stirring for 5 h. The mixture was treated with a solution of concentrated H_2SO_4 (0.55 ml) in EtOH (2 ml) and refluxed with stirring for 2 h. The obtained precipitate was filtered, washed with EtOH (10 ml), hot H_2O (40 ml) and finally with EtOH (10 ml), and dried at 100 °C.

3-(4,5-Dimethoxy-2-nitrophenyl)coumarin (**6a**). Yellow crystals. IR (KBr): 3040, 3004, 2947, 2851, 1717, 1512, 1335, 1278, 1222, 1069, 875, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 3H, MeO), 3.94 (s, 3H, MeO), 7.25 (s, 1H), 7.41 – 7.46 (m, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.65 – 7.70 (m, 1H), 7.73 (s, 1H), 7.80 (dd, J = 7.7, 1.3 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.2, 56.5, 107.9, 114.3, 116.1, 119.1, 123.9, 124.9, 126.8, 128.6, 132.0, 140.2, 140.6, 148.6, 152.8, 152.9, 159.0; Anal. Calcd for $C_{17}H_{13}NO_6$: C, 62.39; H, 4.00; N, 4.28. Found: C, 62.29; H, 3.93; N, 4.27.

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12. *Crystal data for **9a**:* Yellow crystals 0.25×0.12×0.04 mm, θ < 28.28°, 7428 reflections were collected, 3624 independent reflections (R_{int} 0.0181), completeness 98.9%. Crystal is triclinic, space group P-1, a= 6.6935(9) Å, b= 7.5212(7) Å, c= 15.399(2) Å, α= 76.398(10), β= 82.687(11)°, γ= 81.040(10)°, μ= 0.113 mm^{-1}. The SHELXTL program[16] was used for solution and structure refinement. The details of the refinement and the final R indices: R_1= 0.0354 [I>2σ(I)], wR_2= 0.0880 [I>2σ(I)], R_1= 0.0696 (all data), wR_2= 0.0927 (all data), S= 1.001. Deposition number CCDC 939607 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

13. Mercury 3.1, available from http://www.ccdc.cam.ac.uk/mercury/.

14. General procedure for the preparation of indolo[3,2-*c*]coumarins [chromeno[4,3-*b*]indol-6(11*H*)-ones] **7**. The appropriate coumarin **6** (1 mmol), Ph_3P (3 mmol, 0.8 g) or $(EtO)_3P$ (3 mmol, 0.5 ml) and diglyme (2.5 ml) were placed in a reaction vessel. The resulting suspension was irradiated[17] with stirring at 200 °C (250 W) for 25 min. The mixture was cooled and the product was filtered, washed with diglyme (3 ml) and EtOH (10 ml), and dried at 110 °C.

8,9-Dimethoxychromeno[4,3-*b*]indol-6(11*H*)-one (**7a**). Light cream powder. IR (KBr): 3201, 3001, 2958, 2839, 1704, 1669, 1511, 1486, 1454, 1294, 1207, 1152, 1107, 1017, 842, 752, 537 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H, MeO), 3.89 (s, 3H, MeO), 7.15 (s, 1H), 7.42 – 7.53 (m,

3H), 7.54 – 7.61 (m, 1H), 8.15 (dd, *J* = 7.8, 1.1 Hz, 1H), 12.79 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.7, 55.8, 95.7, 100.2, 101.7, 113.5, 116.9, 117.0, 122.0, 124.2, 129.8, 132.1, 139.9, 146.5, 148.5, 152.1, 158.0; Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.39; H, 4.57; N, 4.74.

15. *Crystal data for* ***9a****:* White crystals 0.25×0.20×0.15 mm, θ < 26.37°, 5235 reflections were collected, 4315 independent reflections (R_{int} 0.0293), completeness 96.7%. Crystals belong to the triclinic space group P-1, a= 7.9538(10) Å, b= 10.5329(17) Å, c= 14.242(2) Å, α= 68.751(12)°, β= 87.641(15)°, γ= 80.276(12)°, μ= 0.080 mm^{-1}. The SHELXTL program[16] was used for solution and structure refinement. The details of the refinement and the final R indices: R_1= 0.0512 [I>2σ(I)], wR_2= 0.1475 [I>2σ(I)], R_1= 0.1351 (all data), wR_2= 0.1518 (all data), S= 1.001. Deposition number CCDC 939608 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

16. Sheldrick, G. M. *Acta Cryst. Sect. A.* **2008**, *64*, 112 – 122.

17. Microwave experiments were carried out in a Discover unimodal microwave system (CEM, USA) with a working frequency of 2.45 GHz and the power of microwave radiation ranged from 0 to 300 W. The reactions were carried out in a 10 ml reaction tube fitted with a Teflon stopper. The temperature of the reaction was monitored with an internal IR sensor located on the external surface of the reaction vessel.

Graphical abstract

A convenient approach to the design and synthesis of indolo[3,2-*c*]coumarins via the microwave-assisted Cadogan reaction

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