Facile Preparation of 3-Amino-4-(arylamino)-1*H*-isochromen-1-ones by a New Multicomponent Reaction

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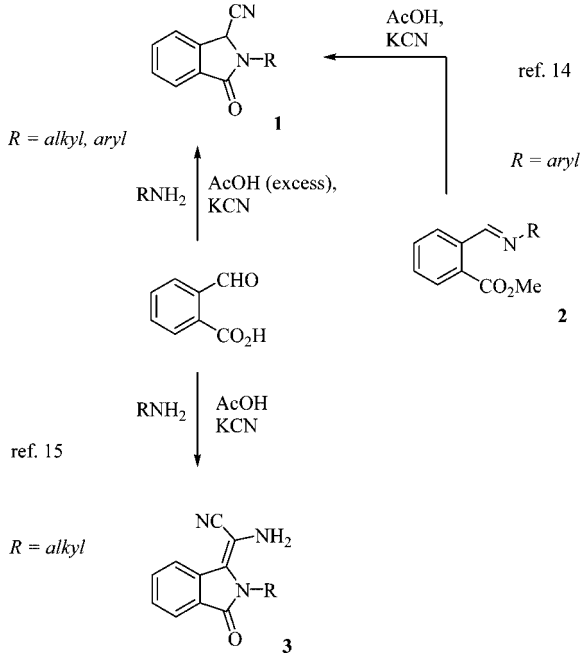
Reactions between 2-formylbenzoic acid, various anilines and HCN result in the formation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones in high yield. The mechanism of this three-component condensation involves the intermediate formation of an α-aminonitrile and subsequent cyclization through nucleophilic attack of the *ortho*-carboxylate at the nitrile carbon.

Introduction

Multicomponent reactions (MCRs) are valuable tools for the preparation of complex structures from simple starting materials. In particular, they are well suited for the rapid and highly atom-economical assembly of large compound libraries. Consequently, the application of MCRs in the drug discovery process has enjoyed considerable attention, and the development of new MCRs is being pursued both in industry and academia.[1,2] From the discovery of the Strecker reaction in 1850,[3] the repertoire has expanded to include a multitude of synthetic procedures, among them, for example, the Hantzsch pyrrole and dihydropyridine synthesis,[4,5] the Mannich reaction,[6] the Biginelli condensation,[7] the Passerini reaction,[8] and the Petasis reaction.[9] Whereas a relatively large proportion of the known MCRs are based on isonitriles, the prototype being the Ugi four-component condensation,[10] only a few MCRs employ hydrogen cyanide as reactant. On the other hand, two HCN-based reactions, the Strecker reaction and the related Bucherer–Bergs hydantoin synthesis,[11,12] are important industrial processes used for the production of amino acids or chelators such as EDTA or NTA on a 100000-ton scale. Here we report on a novel three-component condensation of 2-formylbenzoic acid with anilines and hydrogen cyanide to afford 3-amino-4-(arylamino)-1*H*-isochromen-1-ones.

Results and Discussion

Reactions between 2-formylbenzoic acid, amines and HCN have turned out to be a surprisingly rich source of different heterocyclic products. In the presence of an excess of acid, 2-substituted 3-oxoisoindoline-1-carbonitriles **1** are formed through cyclodehydration of the intermediate α-aminonitriles.[13] Products of the same type have been prepared by Baum and Staveski from Schiff bases of methyl 2-formylbenzoate (Scheme 1).[14]



Scheme 1. Synthesis of amino(3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitriles and 3-oxoisoindoline-1-carbonitriles.

Recently, we found that amino(3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitriles **3** can be obtained from 2-formylbenzoic acid, HCN and α-unbranched primary amines under neutral or basic conditions.[15] In contrast to the formation of compounds **1**, this reaction is rather sensitive to the steric bulk of the amine component, even an isopropyl group preventing the corresponding product from being

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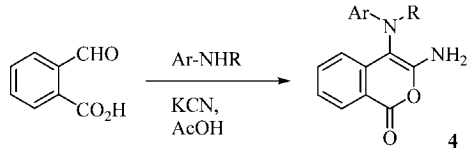
formed. Consequently, treatment of 2-formylbenzoic acid with anilines does not yield compounds of type **3**. In the presence of an excess of acetic acid, the dehydrated Strecker products **1** were obtained instead. When the same reaction was run with an equimolar mixture of aniline and acetic acid, however, a yellow crystalline compound was obtained, with the same composition as the Strecker product as judged by mass spectrometry and elemental analysis, but not showing any C≡N absorption in the IR spectrum. NMR analysis revealed this substance to be 3-amino-4-(phenylamino)-1*H*-isochromen-1-one (**4a**). To explore the scope of this novel three-component condensation, a set of substituted anilines was subjected to the same conditions; the results are listed in Table 1.

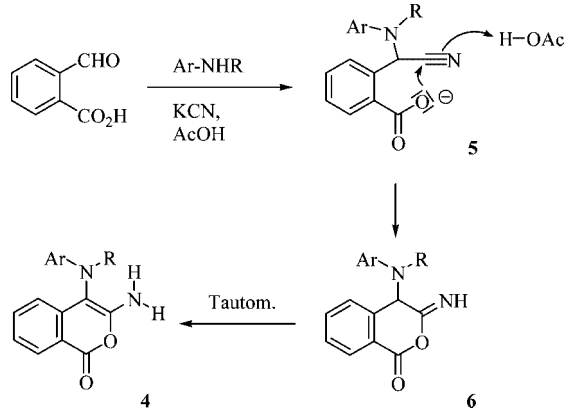
Table 1. Preparation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones.



4

Compound	Ar	R	Yield (%)
4a	Ph	H	82
4b	2-Me-C_6H_4	H	75
4c	3-Me-C_6H_4	H	60
4d	4-Me-C_6H_4	H	82
4e	3-MeO-C_6H_4	H	88
4f	4-MeO-C_6H_4	H	78
4	4-CF_3-C_6H_4	H	81
4h	4-Br-C_6H_4	H	74
4i	4-Cl-C_6H_4	H	87
4j	Ph	Me	64
4k	2,4-Me_2-C_6H_3	H	56

In all cases, the 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **4** could be isolated in high yield from the reaction mixtures as stable yellow crystalline solids. The mechanism of their formation can be interpreted as depicted in Scheme 2. Firstly, a regular Strecker reaction at the aldehyde function takes place. Subsequently, the nitrile carbon of the intermediate α-aminonitrile **5** is nucleophilically attacked by the carboxy group to yield the *O*-acyl imidate **6**, followed by tautomerization to **4**.



Scheme 2. Proposed mechanism of the formation of compounds **4**.

This MCR therefore has a certain similarity to the Bucherer–Bergs reaction, with the *ortho*-carboxy group functioning in place of the carbamate, though the final imidate–amide rearrangement step does not take place. The reaction appears to be much less sensitive to the steric bulk of the amine component than the formation of compounds **3**, even *N*-methylaniline proving to be a suitable substrate. Although the decisive role of the nature of the amine for the outcome of the reaction is not well understood, it may be argued that the electrophilicity of the nitrile carbon in **5**, and hence the aptitude for a nucleophilic attack by the carboxylate, is increased by an *N*-aryl substituent, thus favouring the formation of compound **4**. Alternatively, the higher pK_a of an alkyl-substituted amino group may give rise to a zwitterionic structure of the aminonitrile **5**, which adopts a different conformation with the nitrile group turned away from the potential nucleophile. At lower pH, however, cyclodehydration of the intermediate aminonitrile to 3-oxoisoindoline-1-carbonitriles **1** becomes the dominant process.

The structural features of the unprecedented diaminoisocoumarin moiety in compounds **4** can be recognized in the crystal structure of the *p*-tolyl derivative **4d** (Figure 1). Steric repulsion between the protons at C(9) and N(11) with

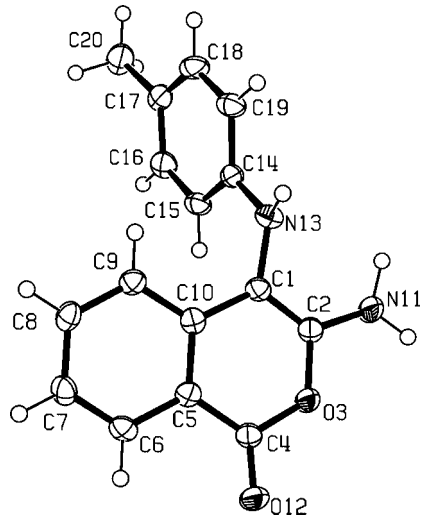


Figure 1. ORTEP view of **4d** at 193 K with the atomic numbering scheme. Thermal ellipsoids are drawn at 50% probability.

Table 2. Selected bond lengths (Å) and angles (°) for **4d**.

Bond lengths		Bond lengths	
C(1)–C(2)	1.346(4)	O(3)–C(4)	1.386(3)
C(1)–C(10)	1.443(3)	C(4)–C(5)	1.439(4)
C(2)–N(11)	1.354(3)	C(4)–O(13)	1.212(3)
C(2)–O(3)	1.372(3)	C(1)–N(13)	1.426(3)
Bond angles		**Bond angles**	
C(1)–C(2)–N(11)	126.9(2)	C(2)–O(3)–C(4)	121.6(2)
C(1)–C(2)–O(3)	122.7(2)	O(12)–C(4)–O(3)	115.1(2)
C(2)–C(1)–N(13)	117.6(2)	O(12)–C(4)–C(5)	127.7(2)

the *ortho*-protons of the aniline ring results in a twisted geometry with an angle of 70° between the ring planes. As would be expected, the C(1)=C(2) bond (1.346 Å) shows double bond character and all other bond lengths and angles are within the normal ranges (Table 2). The molecules form a network of inversion symmetric dimers with N(11)–H(11A)···O(12)′ and N(13)–H(13)···N(11)′′ hydrogen bonds.

Compounds **4** present a hydrogen bond "donor-acceptor-acceptor" pattern similar to that found in cytosine, so the ability to form Watson–Crick-type base pairs with guanine might be anticipated (Figure 2). It should be noted that the sp^3-hybridized oxygen O3 is not expected to show a preference for an H-bond donor located outside the ring plane.[16,17] Investigations on this issue are underway in our laboratory.

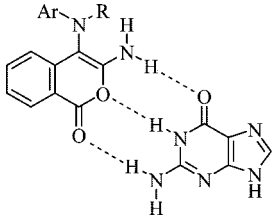


Figure 2. Possible hydrogen bonds between compounds **4** and guanine

Conclusions

In summary, a novel three-component condensation of 2-formylbenzoic acid with anilines and hydrocyanic acid has been found. The reaction furnishes 3-amino-4-(arylamino)-1*H*-isochromen-1-ones in high yield. The ease of their preparation from readily available chemicals should make these compounds attractive starting materials for the preparation of fused heterocycles.

Experimental Section

All reactions were carried out in dried glassware under argon unless stated otherwise. Methanol was dried with magnesium and distilled and stored under nitrogen. Analytical TLC was performed on aluminium backed TLC plates coated with aluminium oxide N/UV_{254} (Macherey–Nagel). Compounds were viewed under UV light (254 nm) and/or by dipping the plates in an alkaline $KMnO_4$ solution and heating. Column chromatography was performed on silica gel (40–63 μm, E. Merck). NMR spectra were recorded with Bruker AC 300 or AMX 400 spectrometers; chemical shifts were referenced to the residual solvent peak ([D$_6$]DMSO, δ_H = 2.50 ppm, δ_C = 39.43 ppm). Coupling constants were partly determined by Lorentz–Gauss transformation. ^{13}C NMR spectra were recorded with broad-band ^{1}H decoupling; if necessary, signals were assigned through DEPT-135, gs-COSY-90, gs-HMQC and gs-HMBC spectra. FD-MS spectra were recorded with a Finnigan MAT 95 (desorption voltage 5 kV, heater current 10 mA min^{-1}), the signals of the ^{13}C isotopomers are not given. IR spectra were measured with a Perkin–Elmer 1760X FTIR spectrometer. Elemental analyses were performed with a CHN Rapid (Heraeus). Melting points were measured with a Dr. Tottoli apparatus (Büchi) and are uncorrected. All compounds showed decomposition rather than melting at the given temperatures.

General Procedure: The corresponding aniline (20 mmol), acetic acid (1.14 mL, 20 mmol) and potassium cyanide (0.78 g, 12 mmol) were added to a stirred solution of 2-formylbenzoic acid (1.50 g, 10 mmol) in methanol (25 mL). The resulting mixture was heated to reflux for 3 h. After cooling, the crystalline product was collected by filtration, washed with water and methanol and dried over P_4O_{10}. In cases of incomplete or lacking crystallization, water and CH_2Cl_2 (30 mL each) were added to the residue, the organic layer was separated, washed with satd. aq. $NaHCO_3$ and dried with Na_2SO_4, and the solvent was removed in vacuo. The resulting residue was purified by flash chromatography or recrystallization.

3-Amino-4-phenylamino-1*H*-isochromen-1-one (4a): Yellow crystals (2.08 g, 82%), m.p. 131 °C (dec.), R_f (cyclohexane/EtOAc/CH_2Cl_2 2:1:1) = 0.48. ^{1}H NMR (300 MHz, [D$_6$]DMSO), COSY (400 MHz, [D$_6$]DMSO): δ = 6.50–6.62 (m, 5 H, NH_2, 2′,6′-H, 4′-H), 6.80 (s, 1 H, NH), 7.02–7.11 (m, 4 H, 5-H, 7-H, 3′,5′-H), 7.52 (ddd, J = 8.3, 7.2, 1.3 Hz, 1 H, 6-H), 7.92 ppm (pseudo-d, J = 7.9 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO), HMQC, HMBC (400/100.6 MHz, [D$_6$]DMSO): δ = 90.5 (C-4), 112.7 (C-2′,6′), 113.9 (C-8a), 116.7 (C-4′), 119.6 (C-5), 122.1 (C-7), 128.9 (C-3′,5′), 129.2 (C-8), 134.8 (C-6), 141.7 (C-4a), 147.7 (C-1′), 156.0 (C-3), 160.3 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3474, 3375, 3300, 1728, 1653, 1605, 1586, 1497, 1483, 1304, 766, 756, 696 cm^{-1}. FD-MS (*m*/*z*): 252.2 (100) [M]$^+$, 504.7 (5) [2M]$^+$. $C_{15}H_{12}N_2O_2$ (252.27): calcd. C 71.42, H 4.79, N 11.10; found C 71.61, H 4.93, N 11.24.

3-Amino-4-(2-tolylamino)-1*H*-isochromen-1-one (4b): Yellow crystals (2.00 g, 75%), m.p. 150 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.55. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.32 (s, 3 H, Me), 6.09 (s, 1 H, NH), 6.18 (dd, J = 8.1, 1.1 Hz, 1 H, 6′-H), 6.48–6.55 (m, 3 H, NH_2, 4′-H), 6.83 (d-pseudo-t, J_t = 8, J_d = 1.7 Hz, 5′-H), 6.94–7.10 (m, 3 H, 5-H, 7-H, 3′-H), 7.49 (ddd, J = 8.1, 7.2, 1.4 Hz, 1 H, 6-H), 7.92 ppm (pseudo-d, J = 8.1 Hz, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 17.8 (Me), 90.5 (C-4), 110.3 (C-6′), 113.9 (C-8a), 116.6 (C-4′), 119.7 (C-5), 122.1 (C-7), 122.2 (C-2′), 126.5 (C-5′), 129.2 (C-8), 130.0 (C-3′), 134.7 (C-6), 141.7 (C-4a), 145.1 (C-1′), 155.9 (C-3), 160.4 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3476, 3397, 3326, 1729, 1641, 1604, 1550, 1503, 1484, 1268, 984, 763, 750 cm^{-1}. FD-MS (*m*/*z*): 266.4 (100) [M]$^+$, 533.0 (5) [2M]$^+$. $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H 5.30, N 10.52; found C 71.97, H 5.26, N 10.34.

3-Amino-4-(3-tolylamino)-1*H*-isochromen-1-one (4c): The product was purified by flash chromatography on silica gel with cyclohexane/EtOAc 5:2 as the eluent. Yellow crystals (1.61 g, 60%), m.p. 152 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.51. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.15 (s, 3 H, Me), 6.34–6.44 (m, 3 H, 2′-H, 4′-H, 6′-H), 6.52 (s, 2 H, NH_2), 6.72 (s, 1 H, NH), 6.93 (t, J = 7.9 Hz, 1 H, 5′-H), 7.04–7.11 (m, 2 H, 5-H, 7-H), 7.51 (ddd, J = 8.1, 7.2, 1.4 Hz, 1 H, 6-H), 7.90 ppm (pseudo-d, J = 7.8 Hz, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 21.2 (Me), 90.6 (C-4), 110.0 (C-6′), 113.3 (C-2′), 113.9 (C-8a), 117.7 (C-4′), 119.7 (C-5), 122.1 (C-7), 128.8 (C-5′), 129.2 (C-8), 134.8 (C-6), 137.9 (C-3′), 141.8 (C-4a), 147.8 (C-1′), 156.0 (C-3), 160.3 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3463, 3342, 1714, 1632, 1606, 1553, 1481, 1330, 1158, 1294, 771 cm^{-1}. FD-MS (*m*/*z*): 266.4 (100) [M]$^+$, 533.0 (3) [2M]$^+$. $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H 5.30, N 10.52; found C 71.89, H 5.38, N 10.41.

3-Amino-4-(4-tolylamino)-1*H*-isochromen-1-one (4d): The reaction time was only 45 min. Yellow crystals (2.18 g, 82%), m.p. 156–163 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.38. ^{1}H NMR

(300 MHz, [D$_6$]DMSO), COSY (400 MHz, [D$_6$]DMSO): δ = 2.14 (s, 3 H, Me), 6.46–6.51 (m, 4 H, NH$_2$, 2′,6′-H), 6.60 (s, 1 H, NH), 6.86 (AA′ part of AA′XX′, 2 H, 3′,5′-H), 7.02–7.09 (m, 2 H, 5-H, 7-H), 7.49 (ddd, J = 8.2, 7.1, 1.3 Hz, 1 H, 6-H), 7.90 ppm (pseudo-d, J = 7.7 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO), HMQC, HMBC (100.6 MHz, [D$_6$]DMSO): δ = 20.0 (Me), 91.0 (C-4), 112.8 (C-2′,6′), 114.0 (C-8a), 119.7 (C-5), 122.0 (C-7), 125.1 (C-4′), 129.2 (C-8), 129.3 (C-3′,5′), 134.7 (C-6), 141.7 (C-4a), 145.3 (C-1′), 156.0 (C-3), 160.3 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3460, 3369, 3284, 1724, 1650, 1606, 1516, 1482, 1295, 811, 757, 697 cm^{-1}. FD-MS (*m*/*z*): 266.3 (100) [M]$^+$, 532.8 (3) [2M]$^+$. $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H, 5.30, N 10.52; found C 72.34, H 5.23, N 10.65.

3-Amino-4-(3-methoxyphenylamino)-1*H*-isochromen-1-one (4e): Yellow crystals (2.49 g, 88%), m.p. 163 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.53. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.63 (s, 3 H, OMe), 6.13–6.22 (m, 3 H, 2′-H, 4′-H, 6′-H), 6.53 (s, 2 H, NH$_2$), 6.82 (s, 1 H, NH), 6.95 (t, J = 8.1 Hz, 1 H, 5′-H), 7.04–7.11 (m, 2 H, 5-H, 7-H), 7.51 (ddd, J = 8.3, 7.1, 1.4 Hz, 1 H, 6-H), 7.90 ppm (ddd, J = 7.9, 1.4, 0.6 Hz, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 54.6 (OMe), 90.5 (C-4), 98.8 (C-2′), 102.1, 105.6 (C-4′, C-6′), 113.9 (C-8a), 119.6 (C-5), 122.1 (C-7), 129.2 (C-8), 129.6 (C-5′), 134.8 (C-6), 141.6 (C-4a), 149.2 (C-1′), 156.0 (C-3), 160.27, 160.31 ppm (CO, C-3′). IR (KBr): $\tilde{\nu}$ = 3409, 3374, 3319, 1714, 1645, 1626, 1551, 1494, 1162, 1093, 845, 748 cm^{-1}. FD-MS (*m*/*z*): 282.4 (100) [M]$^+$. $C_{16}H_{14}N_2O_3$ (282.29): C 68.07, H 5.00, N 9.92; found C 67.96, H 5.09, N 9.97.

3-Amino-4-(4-methoxyphenylamino)-1*H*-isochromen-1-one (4f): Yellow crystals (2.21 g, 78%), m.p. 167 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.56. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.62 (s, 3 H, OMe), 6.45–6.55 (m, 5 H, NH, NH$_2$, 2′,6′-H), 6.70 (AA′ part of AA′BB′, 2 H, 3′,5′-H), 7.04–7.10 (m, 2 H, 5-H, 7-H), 7.50 (ddd, J = 8.3, 7.0, 1.3 Hz, 1 H, 6-H), 7.90 ppm (dd, J = 8.3, 1.3 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 55.2 (OMe), 91.5 (C-4), 113.6, 114.6 (C-2′,6′, C-3′,5′), 114.0 (C-8a), 119.7 (C-5), 122.0 (C-7), 129.2 (C-8), 134.7 (C-6), 141.6, 141.8 (C-4a, C-1′), 151.3 (C-4′), 156.1 (C-3), 160.3 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3433, 3379, 3292, 1718, 1647, 1606, 1511, 1483, 1233, 1032, 825, 754 cm^{-1}. FD-MS (*m*/*z*) = 282.4 (100) [M$^+$]. $C_{16}H_{14}N_2O_3$ (282.29): C 68.07, H 5.00, N 9.92; found C 68.09, H 4.96, N 9.97.

3-Amino-4-[4-(trifluoromethyl)phenylamino]-1*H*-isochromen-1-one (4g): The product was purified by recrystallization from ethyl acetate/cyclohexane. Yellow crystals (2.58 g, 81%), m.p. 152 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.40. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.66–6.72 (m, 4 H, NH$_2$, 2′,6′-H), 7.00 (pseudo-d, J = 8.1 Hz, 1 H, 5-H), 7.08 (ddd, J = 8.1, 7.1, 1.1 Hz, 1 H, 7-H), 7.38 (AA′ part of AA′XX′, 2 H, 3′,5′-H), 7.47 (s, 1 H, NH), 7.53 (ddd, J = 8.1, 7.1, 1.3 Hz, 1 H, 6-H), 7.92 ppm (pseudo-d, J = 8.1 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 89.1 (C-4), 112.4 (br., C-2′,6′), 113.9 (C-8a), 116.6 (q, ^2J(C,F) = 32 Hz, C-4′), 119.2 (C-5), 122.2 (C-7), 125.2 (q, $^1J_{C,F}$ = 270 Hz, CF$_3$), 126.2 (q, $^3J_{C,F}$ = 3.4 Hz, C-3′,5′), 129.4 (C-8), 135.0 (C-6), 141.2 (C-4a), 151.2 (C-1′), 155.9 (C-3), 160.2 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3369, 1713, 1652, 1619, 1485, 1329, 1158, 1110, 1067, 830 cm^{-1}. FD-MS (*m*/*z*): 320.4 (100) [M]$^+$. $C_{16}H_{11}F_3N_2O_2$ (320.27): C 60.00, H 3.46, N 8.75; found C 59.77, H 3.71, N 8.51.

3-Amino-4-(4-bromophenylamino)-1*H*-isochromen-1-one (4h): Yellow crystals (2.45 g, 74%), m.p. 138 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.26. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.53 (AA′ part of AA′XX′, 2 H, 2′,6′-H), 6.61 (br. s, 2 H, NH$_2$), 7.00–7.04 (m, 2 H, NH, 5-H), 7.07 (ddd, J = 8.1, 7.1, 1.0 Hz, 1 H, 7-H), 7.19 (XX′ part of AA′XX′, 2 H, 3′,5′-H), 7.53 (ddd, J = 8.1, 7.1, 1.3 Hz, 1 H, 6-H), 7.90 ppm (pseudo-d, J = 8.1 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 89.9 (C-4), 107.3 (C-4′), 113.9 (C-8a), 114.7 (C-2′,6′), 119.3 (C-5), 122.1 (C-7), 129.3 (C-8), 131.4 (C-3′,5′), 134.9 (C-6), 141.3 (C-4a), 147.1 (C-1′), 156.0 (C-3), 160.2 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3459, 3367, 1709, 1652, 1606, 1554, 1490, 1330, 1288, 815, 764 cm^{-1}. FD-MS (*m*/*z*): 330.4 (100) [M]$^+$, 332.4 (71). $C_{15}H_{11}BrN_2O_2$ (331.16): C 54.40, H 3.35, N 8.46; found C 54.21, H 3.33, N 8.34.

3-Amino-4-(4-chlorophenylamino)-1*H*-isochromen-1-one (4i): Yellow crystals (2.49 g, 87%), m.p. 168 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.44. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.53–6.62 (m, 4 H, NH$_2$, 2′,6′-H), 6.99–7.12 (m, 5 H, NH, 5-H, 7-H, 3′,5′-H), 7.52 (ddd, J = 8.2, 7.1, 1.4 Hz, 1 H, 6-H), 7.91 ppm (ddd, J = 7.9, 1.4, 0.6 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 90.0 (C-4), 113.9 (C-8a), 114.2 (C-2′,6′), 119.4 (C-5), 119.9 (C-4′), 122.1 (C-7), 128.6 (C-3′,5′), 129.3 (C-8), 134.9 (C-6), 141.4 (C-4a), 146.8 (C-1′), 156.0 (C-3), 160.2 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3430, 1723, 1650, 1608, 1556, 1495, 1305, 1089, 816, 766 cm^{-1}. FD-MS (*m*/*z*): 286.4 (100) [M]$^+$, 288.4 (34). $C_{15}H_{11}ClN_2O_2$ (286.71): C 62.84, H 3.87, N 9.77; found C 63.01, H 3.76, N 9.62.

3-Amino-4-(methylphenylamino)-1*H*-isochromen-1-one (4j): The product was purified by flash chromatography on silica gel with cyclohexane/EtOAc 3:1 as the eluent. Yellow crystals (1.71 g, 64%), m.p. 163 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.69. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.16 (s, 3 H, Me), 6.60–6.66 (m, 3 H, 2′,6′-H, 4′-H), 6.70–6.74 (m, 3 H, NH$_2$, 5-H), this multiplet containing 6.71 (br. s, 2 H, NH$_2$), 6.71 (pseudo-d, J = 8.3 Hz, 1 H, 5-H), 7.04–7.16 (m, 3 H, 7-H, 3′,5′-H), 7.48 (ddd, J = 8.3, 7.1, 1.4 Hz, 1 H, 6-H), 7.94 ppm (ddd, J = 7.9, 1.4, 0.6 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 37.2 (Me), 96.4 (C-4), 111.8 (C-2′,6′), 114.1 (C-8a), 116.2 (C-4′), 119.0 (C-5), 122.1 (C-7), 128.9 (C-3′,5′), 129.6 (C-8), 134.9 (C-6), 140.8 (C-4a), 148.0 (C-1′), 155.8 (C-3), 160.2 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3472, 3337, 1746, 1640, 1603, 1548, 1483, 1494, 1318, 763, 752 cm^{-1}. FD-MS (*m*/*z*): 266.5 (100) [M]$^+$. $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H 5.30, N 10.52; found C 72.36, H 5.38, N 10.57.

3-Amino-4-(2,4-dimethylphenylamino)-1*H*-isochromen-1-one (4k): Yellow crystals (1.58 g, 56%), m.p. 151 °C (dec.), R_f (cyclohexane/EtOAc 2:1) = 0.59. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.12 (s, 3 H, 4′-Me), 2.29 (s, 3 H, 2′-Me), 5.92 (s, 1 H, NH), 6.07 (d, J = 8.1 Hz, 1 H, 6′-H), 6.49 (br. s, 2 H, NH$_2$), 6.64 (dd, J = 8.1, 2.2 Hz, 1 H, 5′-H), 6.85 (d, J = 2.2 Hz, 3′-H), 6.95 (pseudo-d, J = 8.3 Hz, 1 H, 5-H), 7.07 (ddd, J = 8.1, 7.1, 1.3 Hz, 1 H, 7-H), 7.50 (ddd, J = 8.3, 7.1, 1.4 Hz, 1 H, 6-H), 7.91 ppm (dd, J = 8.1, 1.4 Hz, 1 H, 8-H). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 17.7 (2′-Me), 19.9 (4′-Me), 90.9 (C-4), 110.5 (C-6′), 113.9 (C-8a), 119.8 (C-5), 122.0 (C-7), 122.2 (C-2′), 124.9 (C-4′), 126.7 (C-5′), 129.1 (C-8), 130.8 (C-3′), 134.7 (C-6), 141.8 (C-4a), 142.7 (C-1′), 155.9 (C-3), 160.4 ppm (CO). IR (KBr): $\tilde{\nu}$ = 3462, 1728, 1645, 1608, 1553, 1508, 1482, 1332, 1299, 761 cm^{-1}. FD-MS (*m*/*z*): 280.4 (100) [M]$^+$, 560.9 (5) [2M]$^+$. $C_{17}H_{16}N_2O_2$ (280.32): C 72.84, H 5.75, N 9.99; found C 72.92, H 5.68, N 10.11.

CCDC-251052 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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