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Ring Contracting Rearrangements of 3-Amino-4-(arylamino)-1*H*-isochromen-1-ones

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Dedicated to Professor Horst Kunz on the occasion of his 65th birthday

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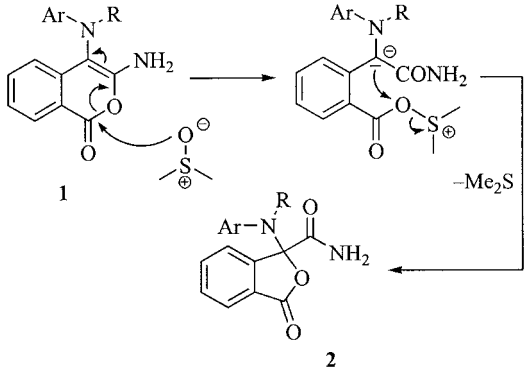
Two new ring contracting rearrangements of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, leading to 1-(arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides and 2-aryl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamides, are described. Both conversions proceed in high yield and no further purification of the products is necessary.

Introduction

Multicomponent reactions (MCRs) belong to the most efficient methods for the preparation of heterocyclic compounds. Some of these processes allow a more direct access to heterocycles of known structure, such as the Bucherer–Bergs reaction,[1–3] the Hantzsch pyrrole synthesis[4] and the Asinger reaction,[5] and often permit the combinatorial variation of the products. In addition to these valuable synthetic shortcuts, MCRs leading to new types of products are constantly being discovered.[6,7] Recently, we found a novel three-component condensation of anilines, 2-formylbenzoic acid and hydrogen cyanide, leading to 3-amino-4-(arylamino)-1*H*-isochromen-1-ones **1**.[8] The products can be isolated in high purity and yield by precipitation from the reaction mixture as yellow crystalline solids. During the investigation of their chemical behaviour, we found two high yielding ring contracting rearrangements on which we report here.

Results and Discussion

When an NMR sample of 3-amino-4-(4-tolylamino)-1*H*-isochromen-1-one (**1d**) in [D_6]DMSO was left to stand at room temperature for a few days, a slow but clean conversion to a single product could be observed. The reaction could be accelerated by raising the temperature and at 70–75 °C, a complete conversion could be achieved in 18–48 h. Analysis of the significantly more polar product by NMR spectroscopy, mass spectrometry and IR spectroscopy revealed this compound to be 3-oxo-1-(4-tolylamino)-1,3-dihydroisobenzofuran-1-carboxamide (**2d**), which originated from an oxidative ring contracting rearrangement. The proposed mechanism of this reaction is depicted in Scheme 1.



Scheme 1. Proposed mechanism for the formation of compounds **2**.

The lactone ring is opened by nucleophilic attack of a DMSO molecule. In turn, the α-carbon of the resulting amide enolate attacks at oxygen and leads to the elimination of dimethyl sulfide. Further experiments showed that the same transformation can be effected when oxygen is added to a solution of **1d** in ethyl acetate. In this case however, marked differences in reactivity between various substituted substrates **1** occurred, which limit the general applicability of this method. On the other hand, the oxidation with DMSO is reliable and only 3-amino-4-(4-arylamino)-1*H*-isochromen-1-ones with *ortho*-substituted arylamino

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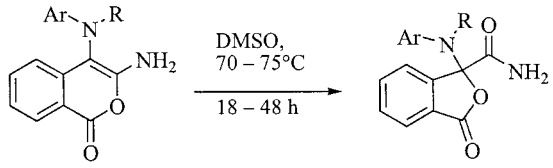
groups such as the 2-tolyl derivative **1b** give product mixtures, presumably due to the tendency of the corresponding products to open the lactone ring (Table 1).

Table 1. Preparation of 1-(arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides **2** by ring contracting oxidation.



1 **2**

Compound	Ar	R	Yield [%]
2a	Ph	H	89
2b	2-Me-C_6H_4	H	[a]
2c	3-Me-C_6H_4	H	68
2d	4-Me-C_6H_4	H	75
2e	3-MeO-C_6H_4	H	80
2f	4-MeO-C_6H_4	H	72
2g	4-CF_3-C_6H_4	H	77
2h	4-Br-C_6H_4	H	70
2i	4-Cl-C_6H_4	H	73
2j	Ph	Me	–

[a] Product mixture.

Unfortunately, no explanation can be given for the lacking reactivity of the *N*-methyl-substituted substrate **1j**. The spectroscopic structural assignment of compounds **2** could be confirmed by the X-ray crystallographic analysis of the 3-methoxy derivative **2e** (Figure 1).[9]

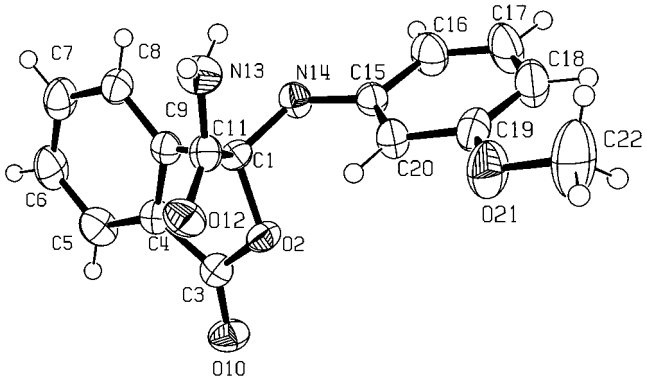
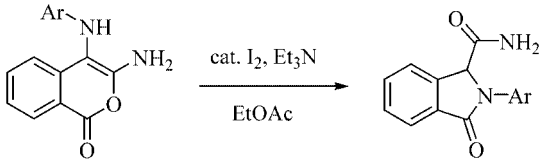


Figure 1. An ORTEP view of compound **2e** (thermal ellipsoids at 50% probability).

A similar aminolactone structure has been proposed for the comparably stable 1-anilino-3-oxo-1,3-dihydroisobenzofuran-1-carboxanilides that have been obtained by treatment of isochroman-1,3,4-triones with aniline.[10,11] In contrast to the conversion of **1** to **2**, this ring contraction does not involve a change of the oxidation state.

When iodine in combination with triethylamine was tested as an alternative oxidant for the conversion of **1d** to **2d**, a colorless crystalline compound with the correct mobility on TLC was formed within a few minutes. A closer investigation of this product revealed however that it was not identical to compound **2d**. Instead, it had the same mass and elemental composition as the starting material. NMR and IR spectroscopy helped to identify the new material as 3-oxo-2-(4-tolylamino)-2,3-dihydro-1*H*-isoindole-1-carboxamide (**3d**). Indeed, catalytic amounts of iodine suffice to convert 3-amino-4-(4-arylamino)-1*H*-isochromen-1-ones **1** to the rearranged products **3** (Table 2).

Table 2. Preparation of 2-aryl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamides **3** by iodine-catalyzed rearrangement.

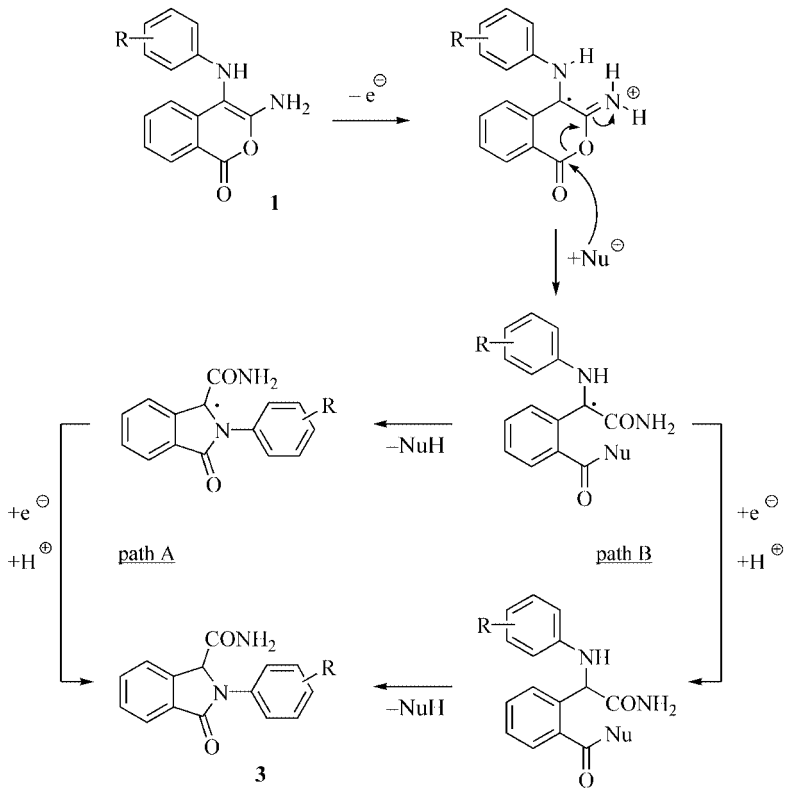


1 **3**

Compound	Ar	Yield [%]
3a	Ph	99
3b	2-Me-C_6H_4	–
3c	3-Me-C_6H_4	93
3d	4-Me-C_6H_4	95
3e	3-MeO-C_6H_4	86
3f	4-MeO-C_6H_4	78
3g	4-CF_3-C_6H_4	61
3h	4-Br-C_6H_4	95
3i	4-Cl-C_6H_4	–

The thermodynamic driving force of the ring contracting rearrangement is obviously the formation of two amide bonds by opening a cyclic *O*-acyl imidate and closure of a five membered lactam ring.[12–15] Surprisingly, we found only two ways to effect this transformation in an appreciable yield. Apart from the I_2/Et_3N system, Cu^{2+} salts such as $CuBr_2$ and $CuCl_2$ catalyze the formation of compounds **3**. On the other hand, salts of other divalent cations like Zn^{2+} and Ni^{2+} or nucleophilic catalysts such as cyanide or DMAP do not yield the rearranged lactams. Therefore, the mechanism of the formation of compounds **3** presumably involves two single-electron transfer steps as shown in Scheme 2.

After the single electron oxidation of the electron-rich enediamine moiety,[16,17] the lactone ring of the resulting radical cation could be opened by a nucleophile. The resulting radical should then, either before or after closure of the five membered lactam ring, be reduced and reprotonated to furnish the product **3**. While steric repulsion might be responsible for the failure of the ring contraction on substrates with *ortho*-substituted aryl groups (e.g. **1b**), we do not have a satisfactory explanation for the deviant behaviour of the 4-Cl derivative **1i**.



Scheme 2. Proposed mechanism of the formation of compounds **3**.

Conclusions

In summary, we have found two novel ring-contracting rearrangements of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones, yielding 1-(arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides and 2-aryl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamides, respectively. The driving force for both reactions is the formation of a primary amide from a cyclic *O*-acyl imidate. Apparently, an oxidative step is required to effect the opening of the electron-rich diaminopyran-2-one ring. The reported findings demonstrate that the easily accessible 3-amino-4-(arylamino)-1*H*-isochromen-1-ones are valuable starting materials for the preparation of other heterocyclic compounds.

Experimental Section

All reactions were carried out under an inert atmosphere of argon unless stated otherwise. NMR spectra were recorded on a Bruker AC-300 or AMX-400 spectrometer, 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 via Lorentz–Gauss transformation. ^{13}C NMR spectra were recorded with ^{1}H broad band decoupling; if necessary, signals were assigned based on DEPT-135, gs-COSY-90, gs-HMQC, and gs-HMBC spectra. Two-dimensional NMR spectra were measured at 400 MHz. FD-MS spectra were recorded on a Finnigan MAT 95 at a desorption voltage of 5 kV using a heater current ramp of 10 mA/min. IR spectra were measured on a Perkin–Elmer 1760X FTIR spectrometer. Melting points were measured on a Dr. Tottoli apparatus (compounds **2**) or on a Kofler apparatus (compounds **3**) and are uncorrected. The products did not have sharp melting points but rather started decomposing at the given temperatures; the values depend on the heating rate. Elemental analyses were performed on a CHN Rapid (Heraeus).

Preparation of 1-(Arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides 2. General Procedure: A stirred solution of the 3-amino-4-(arylamino)-1*H*-isochromen-1-one **1** (1.0 mmol) in DMSO (10 mL) was heated to 70–75 °C under an argon atmosphere. After TLC indicated complete conversion of the starting material, the mixture was cooled, poured on ice (ca. 50 g) and after 1 h, the precipitate was collected by filtration. After washing with diethyl ether (ca. 25 mL), the material was dried in vacuo. The obtained products were analytically pure and required no further purification steps.

1-Anilino-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2a): From 3-amino-4-anilino-1*H*-isochromen-1-one (**1a**) (292 mg, 1.16 mmol) in 2d at 75 °C. Yield: 276 mg (89%) of a colorless powder, m.p. 194 °C dec. IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (br), 1763, 1693, 1606, 1500, 1290, 1251, 1113, 924, 750, 694 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.76–6.85 (m, 3 H, H4′, H2′,6′), 7.18 (pseudo-dd, J_{app} = 8.8, 7.2 Hz, 2 H, H3′,5′), 7.51 (s, 1 H, ArNH), 7.60 (s, 1 H, CONH^b), 7.73 (pseudo-t, J_{app} = 7.4 Hz, 1 H, H5), 7.84–7.94 (m, 3 H, H4, H6, H7), 8.10 (s, 1 H, CONH^a) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 94.8 (C1), 115.7 (C2′,6′),119.3 (C4′), 123.6 (C7), 124.9 (C4), 126.0 (C3a), 128.6 (C3′,5′), 131.0 (C5), 134.7 (C6), 143.7 (C1′), 146.4 (C7a), 168.1 ($CONH_2$), 168.5 (C3) ppm. FD-MS (*m*/*z*): M$^+$ 268.4 (100%). $C_{15}H_{12}N_2O_3$ (268.27): calcd. C 67.16, H 4.51, N 10.44; found 66.94, H 4.41, N 10.41.

3-Oxo-1-(3-tolylamino)-1,3-dihydroisobenzofuran-1-carboxamide (2c): From 3-amino-4-(3-tolylamino)-1*H*-isochromen-1-one (**1c**) (256 mg, 0.96 mmol) in 2d at 75 °C. Yield: 185 mg (68%) of an off-white powder, m.p. 186 °C dec. IR (KBr): $\tilde{\nu}$ = 3445, 3323, 1765,

1742, 1693, 1612, 1598, 1494, 1293, 1258, 1114, 920, 693 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.22 (s, 3 H, Me), 6.59–6.67 (m, 3 H, H2′, H4′, H6′), 7.06 (t, J = 7.7 Hz, 1 H, H5′), 7.44 (s, 1 H, ArNH), 7.60 (s, 1 H, CONH[b]), 7.72 (ddd, J = 7.6, 6.9, 1.5 Hz, 1 H, H5), 7.84–7.93 (m, 3 H, H4, H6, H7), 8.08 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 21.3 (Me), 94.9 (C1), 113.1, 116.4 (C2′, C6′), 120.2 (C4′), 123.6 (C7), 124.8 (C4), 126.0 (C3a), 128.5 (C5′), 131.0 (C5), 134.6 (C6), 137.6 (C3′), 143.7 (C1′), 146.5 (C7a), 168.2 ($CONH_2$), 168.6 (C3) ppm. FD-MS (m/z): M^+ 282.5 (100%). $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.07, H 5.00, N 9.92; found 67.99, H 4.87, N 9.81.

3-Oxo-1-(4-tolylamino)-1,3-dihydroisobenzofuran-1-carboxamide (2d): From 3-amino-4-(4-tolylamino)-1*H*-isochromen-1-one (**1d**) (89 mg, 0.33 mmol) in 18 h at 70 °C. Yield: 71 mg (75%) of a yellowish powder, m.p. 192 °C dec. IR (KBr): $\tilde{\nu}$ = 3417, 3326, 3205, 1761, 1677, 1523, 1302, 1284, 1250, 1107, 886, 806 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO), HMQC, HMBC δ = 2.19 (s, 3 H, Me), 6.72 (BB′ part of AA′BB′ system, 2 H, H2′,6′), 6.98 (AA′-part of AA′BB′ system, 2 H, H3′,5′), 7.34 (s, 1 H, ArNH), 7.58 (s, 1 H, CONH[b]), 7.72 (pseudo-t, J_{app} = 7.2 Hz, 1 H, H5), 7.82–7.93 (m, 3 H, H4, H6, H7), 8.06 (s, 1 H, CONH[a]) ppm. ^{13}C NMR, (75.5 MHz, [D_6]DMSO), HMQC, HMBC δ = 20.1 (Me), 95.2 (C1), 116,1 (C2′,6′), 123.6 (C7), 124.8 (C4), 126.1 (C3a), 128.1 (C4′), 129.0 (C3′,5′), 131.0 (C5), 134.6 (C6), 141.1 (C1′), 146.5 (C7a), 168.2 ($CONH_2$), 168.6 (C3) ppm. FD-MS (m/z): M^+ 282.5 (100%). $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.07, H 5.00, N 9.92; found 68.14, H 5.26, N 9.94.

1-(3-Methoxyphenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2e): From 3-amino-4-(3-methoxyphenylamino)-1*H*-isochromen-1-one (**1e**) (338 mg, 1.20 mmol) in 2d at 70 °C. Yield: 286 mg (80%) of an off-white powder, m.p. 158 °C dec. IR (KBr): $\tilde{\nu}$ = 3433, 3374, 1745 (sh), 1698, 1606, 1522, 1466, 1289, 1255, 1205, 1167 (sh), 1124, 948, 916, 769, 690 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 3.67 (s, 3 H, OMe), 6.36–6.44 (m, 3 H, H2′, H-4′, H6′), 7.08 (pseudo-t, J_{app} = 7.9 Hz, 1 H, H5′), 7.52 (s, 1 H, ArNH), 7.62 (s, 1 H, CONH[b]), 7.73 (pseudo-t, J_{app} = 7.1 Hz, 1 H, H5), 7.82–7.95 (m, 3 H, H4, H6, H7), 8.10 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 54.7 (OMe), 94.7 (C1), 102.0, 104.5, 108.5 (C2′, C4′, C6′), 123.6 (C7), 124.9 (C4), 125.9 (C3a), 129.4 (C5′), 131.1 (C5), 134.7 (C6), 145.0 (C1′), 146.4 (C7a), 159.7 (C-3′), 168.1 ($CONH_2$), 168.5 (C3) ppm. FD-MS (m/z): M^+ 298.5 (100%). $C_{16}H_{14}N_2O_4$ (298.29): calcd. C 64.42, H 4.73, N 9.39; found 64.41, H 4.87, N 9.24.

1-(4-Methoxyphenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2f): From 3-amino-4-(4-methoxyphenylamino)-1*H*-isochromen-1-one (**1f**) (436 mg, 1.54 mmol) in 2d at 75 °C. Yield: 330 mg (72%) of an off-white powder, m.p. 173 °C dec. IR (KBr): $\tilde{\nu}$ = 3408, 3322, 1762, 1678, 1519, 1469, 1286, 1251, 1168, 1108, 1038, 889, 747, 640 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.67 (s, 3 H, OMe), 6.68–6.83 (m, 4 H, H2′,6′, H3′,5′), 7.16 (s, 1 H, ArNH), 7.59 (s, 1 H, CONH[b]), 7.71 (pseudo-t, J_{app} = 7.3 Hz, 1 H, H5), 7.80–7.93 (m, 3 H, H4, H6, H7), 8.03 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 55.1 (OMe), 95.9 (C1), 114.0, 117.8 (C2′6′, C3′,5′), 123.6 (C7), 124.8 (C4), 126.2 (C3a), 130.9 (C5), 134.6 (C6), 136.9 (C1′), 146.5 (C7a), 153.2 (C4′), 168.1 ($CONH_2$), 168.6 (C3) ppm. FD-MS (m/z): M^+ 298.5 (100%). $C_{16}H_{14}N_2O_4$ (282.29): calcd. C 64.42, H 4.73, N 9.39; found 64.27, H 4.63, N 9.26.

1-(4-Trifluoromethyl-phenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2g): From 3-amino-4-(4-trifluoromethyl-phenylamino)-1*H*-isochromen-1-one (**1g**) (300 mg, 0.94 mmol) in 2d at 75 °C. Yield: 244 mg (77%) of a colorless powder, m.p. 161 °C dec. IR (KBr): $\tilde{\nu}$ = 3431, 1775, 1697, 1679, 1620, 1532, 1324, 1249, 1169, 1118 (sh), 1070, 911, 837, 748 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.96 (XX′ part of AA′XX′ system, 2 H, H2′,6′), 7.56 (AA′-part of AA′XX′ system, 2 H, H3′,5′), 7.69 (s, 1 H, CONH[b]), 7.76 (ddd, J = 7.8, 5.7, 2.7 Hz, 1 H, H5), 7.87–7.96 (m, 3 H, H4, H6, H7), 8.13 (s, 1 H, ArNH), 8.21 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 93.5 (C1), 115.2 (C2′,6′), 119.3 (q, ^2J(C,F) = 32 Hz, C4′), 123.5 (C7), 124.8 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 125.1 (C4), 125.6 (C3a), 126.0 (q, $^3J_{C,F}$ = 3.7 Hz, C3′,5′), 131.3 (C5), 134.9 (C6), 146.0 (C7a), 147.4 (C1′), 167.6 ($CONH_2$), 168.3 (C3) ppm. FD-MS (m/z): M^+ 336.6 (100%). $C_{16}H_{11}F_3N_2O_3$ (336.27): calcd. C 57.15, H 3.30, N 8.33; found 56.97, H 3.31, N 8.18.

1-(4-Bromophenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2h): From 3-amino-4-(4-bromophenylamino)-1*H*-isochromen-1-one (**1h**) (375 mg, 1.13 mmol) in 2d at 70 °C. Yield: 274 mg (70%) of an off-white powder, m.p. 179 °C dec. IR (KBr): $\tilde{\nu}$ = 3429, 3314, 1769, 1679, 1595, 1511, 1495, 1297, 1284, 1248, 1105, 1092, 899, 814, 749, 692 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.76 (XX′ part of AA′XX′ system, 2 H, H2′,6′), 7.37 (AA′-part of AA′XX′ system, 2 H, H3′,5′), 7.64 (s, 1 H, CONH[b]), 7.70–7.77 (m, 2 H, H5, ArNH), 7.85–7.94 (m, 3 H, H4, H6, H7), 8.15 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 94.3 (C1), 110.7 (C4′), 117.7 (C2′,6′), 123.5 (C7), 125.0 (C4), 125.8 (C3a), 131.2 (C5), 131.3 (C3′,5′), 134.8 (C6), 143.2 (C1′), 146.1 (C7a), 167.8 ($CONH_2$), 168.4 (C3) ppm. FD-MS (m/z): M^+ 346.4 (100%), 348.4 (100%). $C_{15}H_{11}BrN_2O_3$ (347.16): calcd. C 51.89, H 3.19, N 8.07; found 51.90, H 3.08, N 7.87.

1-(4-Chlorophenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (2i): From 3-amino-4-(4-chlorophenylamino)-1*H*-isochromen-1-one (**1i**) (263 mg, 0.92 mmol) in 2d at 75 °C. Yield: 202 mg (73%) of an off-white powder, m.p. 162 °C dec. IR (KBr): $\tilde{\nu}$ = 3427, 3312, 1769, 1680, 1600, 1511, 1498, 1297, 1284, 1250, 1106, 1093, 899, 819, 749 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.82 (BB′ part of AA′BB′ system, 2 H, H2′,6′), 7.25 (AA′-part of AA′BB′ system, 2 H, H3′,5′), 7.65 (s, 1 H, CONH[b]), 7.70–7.77 (m, 2 H, H5, ArNH), 7.84–7.94 (m, 3 H, H4, H6, H7), 8.16 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 94.4 (C1), 117.2 (C2′,6′), 123.0 (C4′), 123.5 (C7), 125.0 (C4), 125.8 (C3a), 128.4 (C3′,5′), 131.2 (C5), 134.8 (C6), 142.8 (C1′), 146.2 (C7a), 167.8 ($CONH_2$), 168.4 (C3) ppm. FD-MS (m/z) M^+ 302.5 (100%), 304.5 (31%). $C_{15}H_{11}ClN_2O_3$ (302.71): calcd. C 59.52, H 3.66, N 9.25; found 59.28, H 3.72, N 9.29.

Preparation of 2-Aryl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamides 3. General Procedure: To a stirred solution of the 3-amino-4-(arylamino)-1*H*-isochromen-1-one **1** (0.75 mmol) in ethyl acetate (10 mL) was added iodine (19 mg, 75 μmol) and triethylamine (30 μL, 213 μmol). After 18 h at ambient temperature under an argon atmosphere, water (4 mL) was added to the suspension and the solid was collected from the resulting mixture by filtration. The residue was washed with diethyl ether (20 mL) and dried in vacuo. The obtained products were analytically pure and required no further purification steps.

3-Oxo-2-phenyl-2,3-dihydro-1*H*-isoindole-1-carboxamide (3a): From 3-amino-4-anilino-1*H*-isochromen-1-one (**1a**) (91 mg, 0.36 mmol). Yield: 90 mg (99%) of an off-white powder, m.p. 252 °C dec. IR (KBr): $\tilde{\nu}$ = 3354 cm^{-1} (br), 3173 (br), 1686, 1498, 1396, 1368, 1333, 1297, 1266, 1210, 756, 690 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 5.90 (s, 1 H, H1), 7.19 (pseudo-t, J_{app} = 7.4 Hz, 1 H, H4′), 7.44 (mc, 2 H, H3′,5′), 7.53 (s, 1 H, CONH[b]), 7.60 (ddd, J = 7.5, 6.7, 1.9 Hz, 1 H, H5), 7.66–7.84 (m, 5 H, H4, H6, H7, H2′,6′), 8.12 (s, 1 H, CONH[a]) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 63.9

(C1), 120.2 (C2′,6′), 122.2 (C7), 123.3 (C4), 124.4 (C4′), 128.8 (C3′,5′), 128.9 (C5), 131.6 (C3a), 132.5 (C6), 138.4 (C1′), 140.8 (C7a), 167.0 (C3), 168.5 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 252.2 (100%). $C_{15}H_{12}N_2O_2$ (252.27): calcd. C 71.42, H 4.79, N 11.10; found 71.63, H 4.81, N 10.96.

3-Oxo-2-(3-tolyl)-2,3-dihydro-1*H*-isoindole-1-carboxamide (3c): From 3-amino-4-(3-tolylamino)-1*H*-isochromen-1-one (**2c**) (121 mg, 0.45 mmol). Yield: 113 mg (93%) of an off-white powder, m.p. 222 °C dec. IR (KBr): $\tilde{\nu}$ = 3344 cm^{-1} (br), 3175 (br), 1690, 1683, 1495, 1400, 1370, 1258, 770, 748, 688 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.34 (s, 3 H, Me), 5.87 (s, 1 H, H1), 7.00 (br. d, J = 7.7 Hz, 1 H, H4′), 7.31 (pseudo-t, J_{app} = 7.7 Hz, 1 H, H5′), 7.49–7.74 (m, 6 H, H5–H7, H2′, H6′, $CONH^b$), 7.80 (dt, J_d = 7.4, J_t = 1.1 Hz, 1 H, H4), 8.09 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 21.2 (Me), 63.9 (C1), 117.5 (C6′), 120.9 (C2′), 122.1 (C7), 123.3 (C4), 125.1 (C4′), 128.6 (C5′), 128.9 (C5), 131.7 (C3a), 132.5 (C6), 137.9, 138.3 (C1′, C3′), 140.8 (C7a), 166.9 (C3), 168.5 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 266.2 (100%). $C_{16}H_{14}N_2O_2$ (266.29): calcd. C 72.16, H 5.30, N 10.52; found 71.90, H 5.12, N 10.52.

3-Oxo-2-(4-tolyl)-2,3-dihydro-1*H*-isoindole-1-carboxamide (3d): From 3-amino-4-(4-tolylamino)-1*H*-isochromen-1-one (**1d**) (106 mg, 0.40 mmol). Yield: 101 mg (95%) of an off-white powder, m.p. 230 °C dec. IR (KBr): $\tilde{\nu}$ = 3436 cm^{-1} (br), 1686, 1619 (br), 1515, 1468, 1369, 1296, 1106, 808, 690 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.30 (s, 3 H, Me), 5.84 (s, 1 H, H1), 7.23 (AA′-part of AA′XX′ system, 2 H, H3′,5′), 7.48 (s, 1 H, $CONH^b$), 7.55–7.73 (m, 5 H, H5–H7, H2′,6′), 7.79 (dt, J_d = 7.4, J_t = 1.0 Hz, 1 H, H4), 8.07 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]-DMSO): δ = 20.3 (Me), 64.0 (C1), 120.4 (C2′,6′), 122.2 (C7), 123.3 (C4), 128.9 (C5), 129.1 (C3′,5′), 131.7 (C3a), 132.4 (C6), 133.6 (C1′, C4′), 135.9, 140.8 (C7a), 166.8 (C3), 168.5 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 266.6 (100%). $C_{16}H_{14}N_2O_2$ (266.29): calcd. C 72.16, H 5.30, N 10.52; found 72.22, H 5.40, N 10.40.

2-(3-Methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamide (3e): From 3-amino-4-(3-methoxyphenylamino)-1*H*-isochromen-1-one (**1e**) (119 mg, 0.42 mmol). Yield: 102 mg (86%) of an off-white powder, m.p. 248 °C dec. IR (KBr): $\tilde{\nu}$ = 3432 cm^{-1} (br), 3352 (br), 3181 (br), 1688, 1677, 1607, 1583, 1497, 1390, 1359, 1294, 1260, 1218, 840, 770 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO), HMQC, HMBC δ = 3.78 (s, 3 H, OMe), 5.88 (s, 1 H, H1), 6.78 (dt, J_d = 7.0, J_t = 2.4 Hz, 1 H, H4′), 7.29–7.37 (m, 2 H, H5′, H6′), 7.45–7.49 (m, 1 H, H2′), 7.53 (s, 1 H, $CONH^b$), 7.59 (dt, J_d = 1.7, J_t = 7.4 Hz, 1 H, H5), 7.64–7.75 (m, 2 H, H6, H7), 7.81 (dt, J_d = 7.4, J_t = 1.0 Hz, 1 H, H4), 8.12 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO), HMQC, HMBC δ = 55.0 (OMe), 63.9 (C1), 106.4 (C2′), 109.5 (C4′), 112.2 (C6′), 122.1 (C7), 123.3 (C4), 128.9 (C5), 129.6 (C5′), 131.6 (C3a), 132.6 (C6), 139.6 (C1′), 140.7 (C7a), 159.5 (C3′), 167.0 (C3), 168.5 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 282.2 (100%). $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.07, H 5.00, N 9.92; found 67.85, H 5.08, N 9.67.

2-(4-Methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamide (3f): From 3-amino-4-(4-methoxyphenylamino)-1*H*-isochromen-1-one (**1f**) (128 mg, 0.45 mmol). Yield: 100 mg (78%) of an off-white powder, m.p. 192 °C dec. IR (KBr): $\tilde{\nu}$ = 3337 cm^{-1} (br), 3171 (br), 1689, 1517, 1468, 1402, 1373, 1260, 1184, 1031, 828, 748 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.77 (s, 3 H, OMe), 5.81 (s, 1 H, H1), 7.00 (AA′-part of AA′XX′ system, 2 H, H3′,5′), 7.48 (s, 1 H, $CONH^b$), 7.55–7.72 (m, 5 H, H5–H7, H2′,6′), 7.79 (dt, J_d = 7.5, J_t = 1.0 Hz, 1 H, H4), 8.04 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 55.2 (OMe), 64.4 (C1), 113.9 (C2′,6′), 122.1 (C7), 122.7 (C3′,5′), 123.2 (C4), 128.9 (C5), 131.3, 131.7 (C1′, C3a), 132.2 (C6), 140.9 (C7a), 156.3 (C4′), 166.7 (C3), 168.6 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 282.2 (100%). $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.07, H 5.00, N 9.92; found 67.92, H 5.05, N 9.74.

3-Oxo-2-(4-trifluoromethyl-phenyl)-2,3-dihydro-1*H*-isoindole-1-carboxamide (3g): From 3-amino-4-(4-trifluoromethyl-phenylamino)-1*H*-isochromen-1-one (**1g**) (139 mg, 0.43 mmol). Yield: 85 mg (61%) of an off-white powder, m.p. 154 °C dec. IR (KBr): $\tilde{\nu}$ = 3386 cm^{-1} (br), 1699, 1687, 1612, 1398, 1365, 1339, 1170, 1116, 1080, 1065, 844 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 5.98 (s, 1 H, H1), 7.58–7.65 (m, 2 H, H5, $CONH^b$), 7.70–7.77 (m, 2 H, H6, H7), 7.80–7.87 (m, 3 H, H2′,6′, H4), 8.00 (broad d, J_{app} = 8.6 Hz, 2 H, H3′,5′), 8.21 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 63.7 (C1), 119.5 (C2′,6′), 122.3 (C7), 123.6 (C4), 124.1 (q, $^2J_{C,F}$ = 32 Hz, C4′), 124.2 (q, $^1J_{C,F}$ = 271 Hz, CF_3), 126.1 (q, $^3J_{C,F}$ = 4.0 Hz, C3′,5′), 129.2 (C5), 131.1 (C3a), 133.1 (C6), 140.8 (C7a), 142.0 (C1′), 167.4 (C3), 168.1 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 320.1 (100%). $C_{16}H_{11}F_3N_2O_2$ (320.27): calcd. C 60.00, H 3.46, N 8.75; found 60.20, H 3.70, N 8.49.

2-(4-Bromophenyl)-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamide (3h): From 3-amino-4-(4-bromophenylamino)-1*H*-isochromen-1-one (**1h**) (128 mg, 0.39 mmol). Yield: 121 mg (95%) of an off-white powder, m.p. 232 °C dec. IR (KBr): $\tilde{\nu}$ = 3344 cm^{-1} (br), 3176 (br), 1685, 1613, 1590, 1495, 1469, 1414, 1396, 1360, 1212, 824, 747 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 5.89 (s, 1 H, H1), 7.56–7.76 (m, 8 H, Ar-H, $CONH^b$), 7.82 (dt, J_d = 7.5, J_t = 1.0 Hz, 1 H, H4), 8.14 (s, 1 H, $CONH^a$) ppm. ^{13}C NMR (75.5 MHz, [D_6]-DMSO): δ = 63.8 (C1), 116.4 (C4′), 121.9 (C2′,6′), 122.2 (C7), 123.4 (C4), 129.0 (C5), 131.3 (C3a), 131.6 (C3′,5′), 132.7 (C6), 137.8 (C1′), 140.7 (C7a), 167.0 (C3), 168.2 ($CONH_2$) ppm. FD-MS (*m*/*z*): M^+ 330.1 (100%), M^+ 332.1 (89%). $C_{15}H_{11}BrN_2O_2$ (331.16): calcd. C 54.40, H 3.35, N 8.46; found 54.13, H 3.29, N 8.22.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all products.

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[9] Crystal data for 1-(3-methoxyphenylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamide (**2e**): formula $C_{16}H_{14}N_2O_4$, monoclinic, space group P 2_1, a = 5.3601(7) Å, b = 14.5903(14) Å, c = 9.2293(10) Å, β = 105.685(5)°, V = 694.9(1) $Å^3$, z = 2, D = 1.426 g cm^{-3}. R = 0.056, Rw = 0.1478. The crystal contained only one enantiomer of the racemic com-

pound. The absolute configuration could, however, not be determined. CCDC-281168 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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