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Unexpected intramolecular cyclization of some 2′-aminochalcones to indolin-3-ones mediated by Amberlyst®-15

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ABSTRACT

The intramolecular cyclization of 2′-aminochalcones derived from 2- and 4-pyridinecarboxaldehydes was carried out in the presence of Amberlyst®-15/AcOH media. Unexpectedly, the reaction proceeded through a 5-*exo* process turning into an alternative approach for the synthesis of 2-(pyridinylmethylene)indolin-3-ones.

The dihydro-1*H*-indol-2- or 3-one frameworks are found in diverse natural occurring products such as Donaxaridine[1] or Austamide,[2] but also widely used as synthons in the preparation of biologically interesting compounds such as melatonine analogs[3] and δ-carboline.[4]

Particularly, their arylidene-derivatives are structures of special interest due to the displayed biological activities. For example, compounds in Figure 1 have shown the following properties: **SU5416** (Semaxanib: $R^1 = R^2 = H$)[5] and **SU11248** (Sunitinib: $R^1 = F$, $R^2 = CONHC_2H_4NEt_2$)[6] are potent KDR kinase inhibitors currently in clinical evaluation stage; compound **A432411** (Ar = 4-hydroxy-3-methoxyphenyl) is an efficient synthetic microtubule inhibitor against a variety of human cancer cell lines;[7] the synthetic compound **1** has shown potent antiamnesic activity;[8] and indolin-3-one **2a** and related derivatives have been prepared as substrates for chromogenic detection of esterase activity.[9]

The classical procedure to prepare indolinone arylidene-derivatives, such as **2**, includes both aqueous and non-aqueous base-catalyzed condensation reaction of indolinones such as **3** with aryl aldehydes[9] (see Scheme 1); and, for example, product **2a** (Ar: 4-pyridinyl) was obtained in 83% yield.[10]

Continuing with our studies on the synthesis and chemical transformations of chalcones,[11] we have recently reported the use of the Amberlyst®-15 as an efficient catalyst for the intramolecular cyclization of a variety of 2′-aminochalcones **4** as an

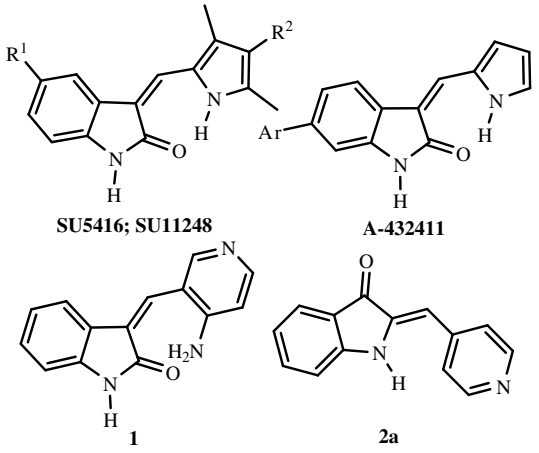
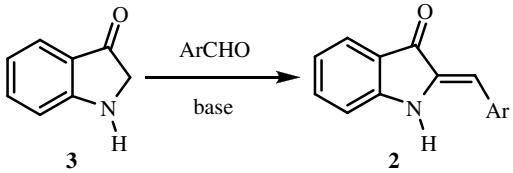


Figure 1.



Scheme 1.

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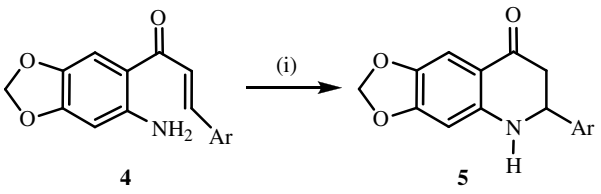
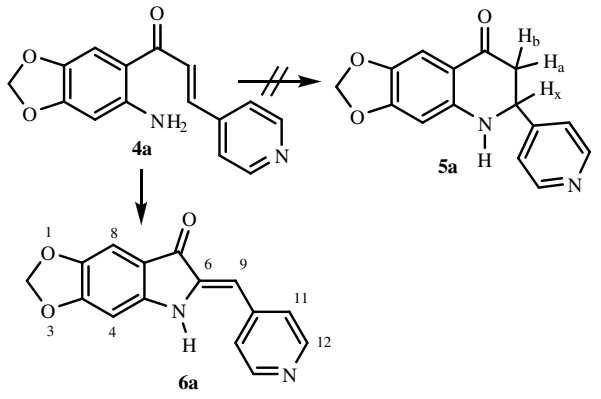


Scheme 2. Reagents and condition:(i) Amberlyst®-15 (10% w/w), AcOH, 80 °C.



Scheme 3.

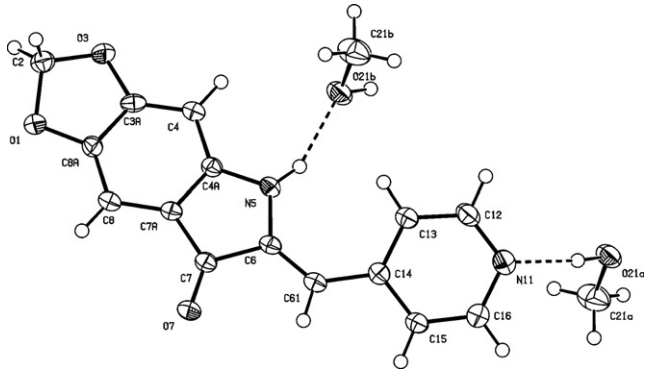


Figure 2. Molecular structure of indolinone **6a** with methanol solvate, showing 30% of probability ellipsoid. Hydrogen bonds between **6a** at (*x*, *y*, *z*) and two different molecules of methanol at (a) (*x*, *y*, 1 + *z*) and (b) (1−*x*, −*y*, 1−*z*) are indicated with dashed lines.

alternative approach toward the synthesis of the hydroquinolin-4-one system **5**,[12,13] as shown in Scheme 2.

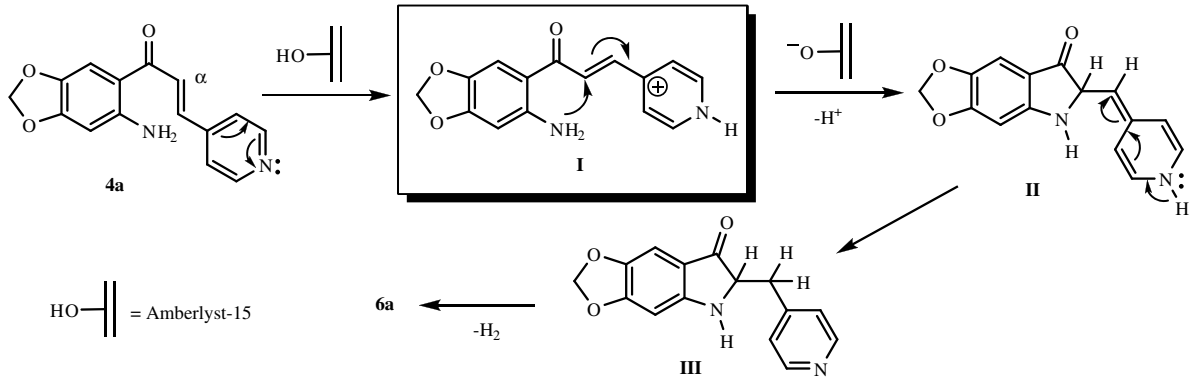
Compounds **5** are pale yellow solids and show fluorescence both in solution and in solid state by irradiation with long-wavelength UV light. Nevertheless, when chalcone **4a** was submitted to the same reaction conditions (i); a non fluorescent dark red solid was obtained as unique product. The spectroscopic evidence showed that typical signals for the expected structure **5a** did not appear (e.g., the absence of the ABX system in ^{1}H NMR), but they are consistent with the tentative indolinone structure **6a**, see Scheme 3.

To confirm the proposed structure for **6a** without ambiguity, single crystals were grown in methanol and solved by X-ray diffraction analysis, which structure is displayed in Figure 2.[14]

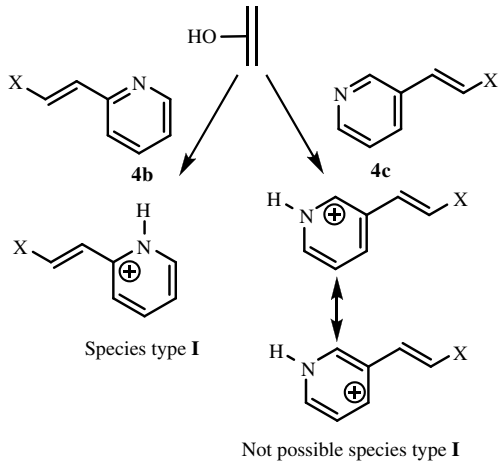
According to this finding, a 5-*exo* cyclocondensation process prevailed over the expected 6-*endo*, specifically for chalcone **4a** but not for the rest of chalcones **4** previously studied.[12] In this sense, indolinone **6a** could have been formed across a mechanism pathway such as that described in Scheme 4. In which the key step is the formation of resonant species **I**, where the *ipso*-carbon atom of the pyridine ring rapidly acquires a positive charge after the protonation of the basic pyridine nitrogen atom. This species **I** is also stabilized via an exocyclic allylic type cation, which favors the 5-*exo* attack of the amino group toward the α-position of **I** originating the species **II** which rapidly tautomerizes to structure **III**. A subsequent dehydrogenation process on the intermediate **III** will generate the isolated compound **6a**. The feasible hydrogen acceptor for the oxidation of **III** should be the ambient oxygen involved in the experimental conditions.

It might suggest that the possible stabilization of a radical intermediate by the pyridine ring is the driving force for this latter process. Similar argument would allow us to predict the formation of the analogous product **6b**, from the isomeric 2-pyridinyl chalcone **4b**, since the formation of a cationic resonant species similar to **I** is completely feasible, favoring again the 5-*exo* process versus the 6-*endo*. In the same way, this proposed sequence might discard the formation of a product type **6** when starting from the isomeric 3-pyridinyl chalcone **4c**, since this position of the nitrogen atom in the pyridine ring does not allow the formation of a stable resonant species like **I**, as depicted in Scheme 5. In this case a 6-*endo* process would be favored and the quinoline **5c** will be the expected product.

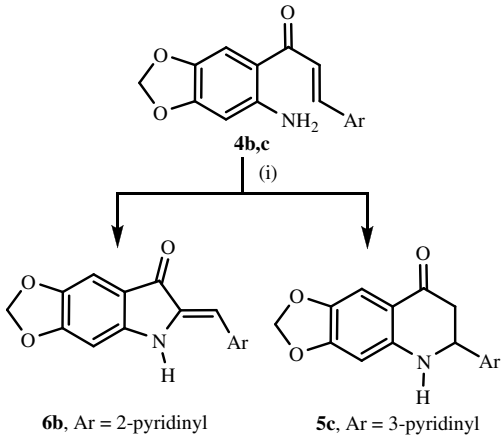
In order to confirm that predicted in Scheme 5, the chalcones **4b** and **4c** were subjected under the same reaction conditions (i), Scheme 6. In the case of chalcone **4b** a dark red solid was obtained again, to which the indolinone structure **6b** was assigned after the spectroscopic analysis, whereas from chalcone **4c** a fluorescent yellow solid was obtained corresponding to the predicted quinoline structure **5c**.[12]



Scheme 4.



Scheme 5.



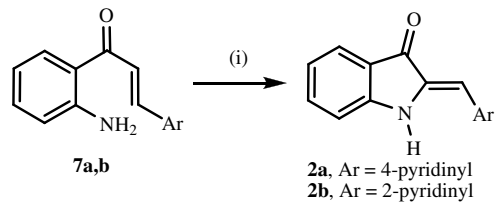
Scheme 6.

These results agree with proposal mechanism (Scheme 4) for the formation of the unexpected indolinones **6**, and the postulated argument to predict formation of **5** or **6** derivatives.

Finally, in order to evaluate the general character of these findings, the chalcones **7a**,**b** were synthesized in 40% and 60% yield, respectively,[13] and submitted to the same reaction conditions (i) to give the expected indolinones **2a** and **2b** (Scheme 7) as the unique products in 65% and 68% yield, respectively.[14]

The somewhat better yields of **6a** over **2a** and **6b** over **2b** structures could be caused by reduction of the positive charge on the carbonyl carbon by resonance with the *para* oxygen of the methylenedioxy group, which also support the proposed key species **I**.

In summary, we are here showing an alternative route for the synthesis of the specific 2-(2- and 4-pyridinylmethylene)indolin-3-ones **2** and **6** in good yields. The formation of products **2** and **6** proceeded across an unexpected 5-*exo* cyclization process which should involve a key resonant species type **I** whose formation is only possible for the 2- and 4-pyridinyl moieties. For the 3-pyridinyl moiety the 6-*endo* process is the preferred one leading to the expected quinoline framework **5**. Although all the reactions were carried out specifically in the Amberlyst®-15/AcOH media, we think that a relatively strong acidity is needed for the protonation of the pyridinyl moieties and so for the formation of the key species **I**, because reaction was not observed when only AcOH was used without the presence of Amberlyst®-15.



Scheme 7.

Acknowledgements

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Supplementary data

All ^{1}H, ^{13}C and DEPT spectra for compounds **2**, **4**, **6**, and **7**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.047.

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13. Data for 1-(6-aminobenzo[1,3]dioxol-5-yl)-3-(pyridin-4-yl)propenone **4a**. This compound was obtained according to Ref. 12. 70% yield. Mp 196–197 °C. IR (KBr): 3355, 3260 (NH_2), 1648 (C=O), 1604 (C=C), 1217 (OCH_2O) cm^{-1}. ^{1}H NMR (400 MHz; DMSO): δ 5.98 (*s*, 2H, OCH_2O), 6.37 (s, 1H), 7.49 (d, 1H, J = 15.45 Hz), 7.68 (s, 1H), 7.79 (br d, 4H, H-pyr (×2) and NH_2), 8.10 (d, 1H, J = 15.42 Hz), 8.61 (d, 2H, J = 5.88 Hz). ^{13}C NMR (100.6 MHz; DMSO): δ 95.8, 101.4 (OCH_2O), 108.1, 109.8, 122.5, 128.3, 138.0, 138.2, 142.5, 150.3, 152.4, 153.3, 187.0 (C=O). EIMS (70 eV): *m/z* (%) = 268 (50, [M^+]), 190 (100, [$M-C_5H_4N$]). Anal. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.25; H, 4.60; N, 10.36. Data for 1-(2-aminophenyl)-3-(pyridin-2-yl)propenone **7b**. 67% yield. Mp 112–115 °C. IR (KBr): 3397, 3274 (NH_2), 1643 (C=O), 1616 (C=N), 1579 (C=C) cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.41 (br s, 2H, NH_2), 6.68–6.72 (m, 2H), 7.26–7.32 (m, 2H), 7.46 (d, 1H, J = 7.76 Hz), 7.70 (d, 1H, J = 14.81 Hz), 7.74 (t, 1H, J = 7.68 Hz), 7.98 (d, 1H, J = 8.40 Hz), 8.20 (d, 1H, J = 15.31 Hz), 8.68 (d, 1H, J = 4.08 Hz). ^{13}C NMR (100.6 MHz; $CDCl_3$): δ 115.9, 117.2, 118.8, 124.0, 125.1, 126.9, 131.6, 134.6, 136.8, 140.9, 150.1, 151.2, 153.6, 191.8. EIMS (70 eV): *m/z* (%) = 224 (33), 223 (27), 195 (67), 146 (100). Anal. Calcd for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 75.09; H, 5.27; N, 12.55.
14. Synthesis of indolinones **2** and **6** according to approach (i). To a solution of chalcone **4** or **7** (0.75 mmol) in AcOH (3–5 mL), the Amberlyst®-15 (10% w/w) was added. The mixture was stirred at 80 °C for 2–5 h until starting material was not detected by TLC. After cooling the solution was filtered, the residue of Amberlyst®-15 was washed with fresh AcOH (3 mL) and recovered. The combined fractions were evaporated under vacuum and the solids were purified from column chromatography on silica gel, by using a mixture of hexanes–AcOEt (5:1) as eluent. Data for (*Z*)-2-(pyridin-4-ylmethylene)-[1,3]dioxolo[4,5-*f*]-indolin-3-one **6a**. 62% yield. Mp 268–270 °C. IR (KBr disk): 3338 (NH), 1676 (C=O), 1595 (C=N), 1275 (OCH_2O) cm^{-1}. ^{1}H NMR (400 MHz,

DMSO): δ 6.11(s, 2H, OCH_2O), 6.44 (s, 1H, H-9), 6.67 (s, 1H, H-4), 7.02 (s, 1H, H-8), 7.60 (d, 2H, J = 4.76 Hz, H-11), 8.61 (d, 2H, J = 4.96 Hz, H-12), 9.86 (br s, 1H, NH). RMN ^{13}C (100.6 MHz, DMSO-d_6): δ 93.6 (C-4), 102.0 (C-8), 102.3 (OCH_2O), 105.3 (C-9), 112.2 (C-7a), 123.4 (C-11), 137.9 (C-6), 141.4 (C-10), 142.8 (C-8a), 150.0 (C-12), 153.6 (C-4a), 155.5 (C-3a), 184.1 (C=O). EIMS (70 eV): m/z (%) = 266 (100) [M$^+$], 265 (94) [M−1]. Anal. Calcd for $C_{15}H_{10}N_2O_3$ (266.25): C, 67.67; H, 3.79; N, 10.52. Found: C, 67.74; H, 3.87; N, 10.44. Crystallographic data for **6a**. MeOH were collected at 120 K on a Bruker Nonius Kappa CCD area diffractometer using MoKα X-ray radiation (λ = 0.71073 Å) and deposit at Cambridge Crystallographic data Center (CCDC reference: 662955). Main crystallographic data are following: Crystal system triclinic, space group $P\bar{1}$, unit cell dimensions: 7.0841(8), 9.840(2), 11.4159(17) Å, 65.420(11)°, 85.354(10)°, 74.143(11)°. Volume 695.6(2) A^3; Z = 2, calculated density 1.424 Mg/m^3, μ = 0.104 mm^{-1}; crystal size 0.11 × 0.32 × 0.58 mm. Range of colletion 3.93° < θ < 27.5°. Reflections collected/unique 13016/3169 [R_{int} = 0.0459]. 98.9% completeness to θ = 27.50. Multi-scan absorption correction SADABS 2.0. T_{Max}/T_{Min} = 0.9886/0.9421. Refinement with SHELXL-97 using a full-matrix least-squares on F^2; S = 1.065; R_1 = 0.0476, wR_2 = 0.1035. $W = [\sigma^2(F_o^2) + (0.0514P)^2 z + 0.3186P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. Data for (*Z*)-2-(pyridin-4-ylmethylene)-1,2-dihydroindolin-3-one **2a**. 65% yield. Mp 204–205 °C. ^{1}H NMR (400 MHz; DMSO-d$_6$): δ = 6.50 (s, 1H), 6.95 (t, 1H), 7.14 (d, 1H), 7.55 (t, 1H), 7.58 (d, 1H), 7.63 (d, 2H), 8.61 (d, 2H), 10.00 (br s, 1H, NH). [lit.[10] 205–206 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 6.51 (s, 1H), 6.96 (t, 1H), 7.15 (d, 1H), 7.57 (t, 1H), 7.61 (d, 1H), 7.65 (d, 2H), 8.63 (d, 2H), 10.05 (s, 1H, NH)]. Data for (*Z*)-2-(pyridin-2-ylmethylene)-1,2-dihydroindolin-3-one **2b**. 68% yield. Mp 135–136 °C. IR (KBr): 3327 (NH), 1695 (C=O), 1605 (C=N) cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ = 6.62 (s, 1H), 6.91 (t, 1H, J = 7.63 Hz), 6.99 (d, 1H, J = 8.07 Hz), 7.14–7.14 (m, 1H), 7.40 (d, 1H, J = 7.84 Hz), 7.46 (t, 1H, J = 7.34 Hz), 7.67–7.72 (m, 2H), 8.67 (d, 1H, J = 4.87 Hz), 9.96 (br s, 1H, NH). ^{13}C NMR (100.6 MHz; $CDCl_3$): δ 105.1, 111.5, 120.0, 120.8, 121.4, 125.1, 126.2, 136.4, 136.5, 138.3, 149.3, 153.2, 155.9, 187.8 (C=O). EIMS (70 eV): m/z (%) = 222 (69) [M$^+$], 221 (67) [M−1]. Anal. Calcd for $C_{14}H_{12}N_2O$ (222.25): C, 75.66; H, 4.54; N, 12.60. Found: C, 75.76; H, 4.63; N, 12.48. (Z)-2-(Pyridin-2-ylmethylene)-[1,3]dioxolo[4,5-*f*]-indolin-3-one **6b**. 75% yield. Mp 233–234 °C. IR (KBr): 3368 (NH), 1676 (C=O), 1605 (C=N), 1248 (OCH_2O) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6): δ = 6.08 (s, 2H, OCH_2O), 6.53 (s, 1H), 6.89 (s, 1H), 6.99 (s, 1H), 7.27–7.31 (m, 1H), 7.64 (d, 1H, J = 7.86 Hz), 7.82 (dt, 1H, J = 7.65 Hz, J = 1.45 Hz), 8.70 (dd, 1H, J = 5.07 Hz, J = 1.45 Hz), 10.1 (br s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 93.9, 101.9, 102.1 (OCH_2O), 105.1, 112.0, 121.9, 126.1, 136.9, 138.1, 145.3, 148.5, 149.5, 154.8, 154.9, 184.5 (C=O). EM (70 eV): m/z (%) = 266 (100) [M$^+$], 265 (8) [M$^+$−1]. Anal. Calcd for $C_{15}H_{10}N_2O_3$ (266.25): C, 67.67; H, 3.79; N, 10.52. Found: C, 67.58; H, 3.72; N, 10.60.