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Versatile reactivity of 3-chloro-2-phenyl-isoindole-1-carbaldehyde: hydrolysis and alkylating rearrangement to 1-amino-4-isochromanones☆

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ABSTRACT

3-Chloro-2-phenyl-isoindole-1-carbaldehyde has been prepared from *N*-phenylisoindolinone under Vilsmeier–Hack conditions. This electrophilic isoindole proved to be stable under the basic conditions used in the final treatment (KOH/MeOH), and for weeks under air in the solid state. Nevertheless, the =C–Cl bond proved highly sensitive to any treatment with reducing or alkylating agents targeted towards the pendant carbaldehyde group, giving various phthalimide derivatives. This unique reactivity is exploited for the selective synthesis of new aminoisochromanones.

1. Introduction

Since their appearance in the chemical scene in 1951,[1] many isoindoles have been synthesized. Quinoid forms of the isoindole nucleus are also found in many natural products and their reported biological activities motivated the search for suitable synthetic strategies.[2] In spite of—and thanks to—their relative instability (in particular for the 2H-isoindole representatives, in equilibrium with their isoindolenine tautomers),[3] the reactivity of isoindoles has been widely investigated, especially in Diels–Alder cycloaddition and electrophilic substitution processes.[3] Only a few examples of nucleophilic substitution on functional derivatives have been described. Halogen replacement in 1,1,3-trichloro-1*H*-isoindole with carboxylic hydrazides was thus reported in 2009,[4] and more recently, the reactivity of 3-halo-2*H*-isoindoles **1** and 3-halo-2-methyl-isoindoles **2** towards carbon, nitrogen, oxygen and sulfur nucleophiles was described by P. Diana et al.[5] As we were at the same time investigating the reactivity of the related 3-chloro-2-phenyl-isoindole substrate **3** (Fig. 1), results evidencing concomitant reactivities of the carbaldehyde and chloroalkene functions of **3** are hereafter presented.

2. Results and discussion

The title substrate, 3-chloro-2-phenyl-isoindole-1-carbaldehyde **3**, was prepared by treatment of the known 1-phenyl-isoindolinone **4** with a $POCl_3$/DMF mixture, thus giving the intermediate isoindoleninium **5**, which finally afforded **3** in 69% yield over two steps after basic hydrolysis using KOH in methanol (Scheme 1).[6] A strong infrared (IR) absorption band at 1614 cm^{-1} is characteristic of the carbaldehyde function of **3**. It is noteworthy that treatment of **4** with $POCl_3$ afforded the acylated 3-chloroisoindole **3** only when DMF was used as the solvent, and not as a stoichiometric reactant.[6]

As no single crystal was suitable for X-ray diffraction analysis, indirect structural information on the carbaldehyde **3**, alternatively described by its aromaticity-stabilized zwitterionic chloroiminium form **A** versus the apolar form **B** (Scheme 2), were tentatively gained from a corresponding Schiff base. Treatment of **3** with *p*-tolylamine in methanol afforded the imino–enamine hydrochloride **6**, resulting from a double condensation at both the carbaldehyde (the targeted Schiff condensation) and chloroalkene moieties (Scheme 2). Whatever the amount of *p*-tolylamine used (one or 2 equiv), **6** was obtained in 51% yield along with

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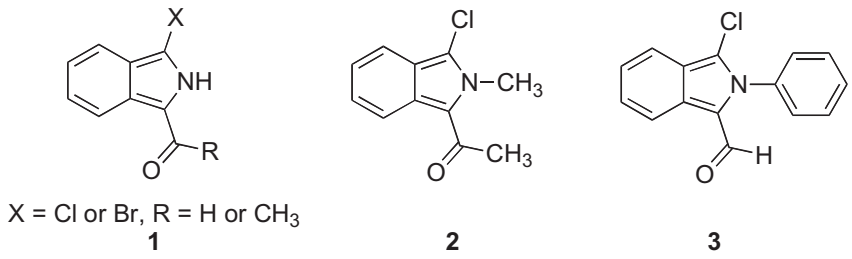
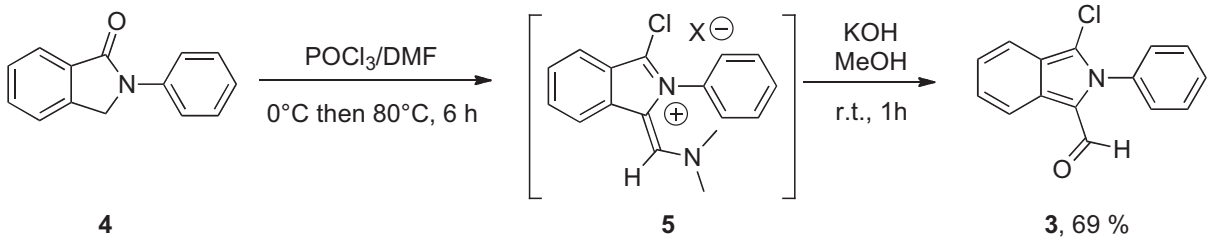
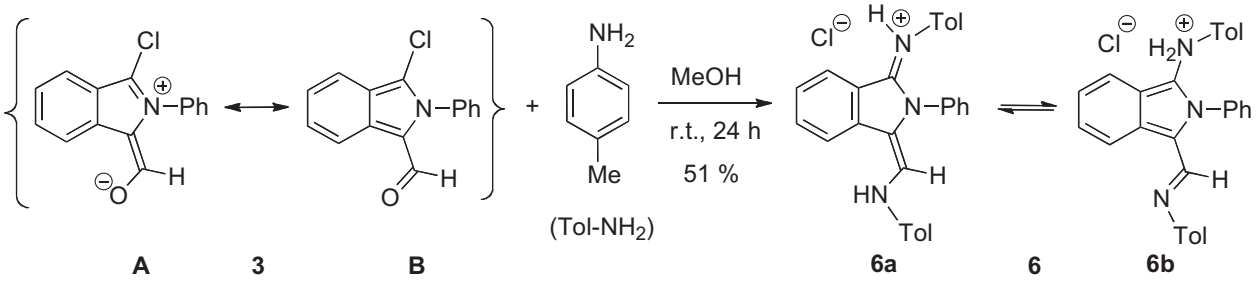


Fig. 1. 1-Acyl-3-halo-isoindole derivatives susceptible to nucleophilic attack.



Scheme 1. Synthesis of 3-chloro-2-phenyl-isoindole-1-carbaldehyde **3**.



Scheme 2. Preparation of the imino–enamine hydrochloride **6**.

unidentified side-products, thus revealing a peculiar sensitivity of the C–Cl bond.

Both the tautomers **6a** and **6b** were observed by ^{1}H NMR spectroscopy in solution, but mono-crystals could be obtained by slow evaporation of a methanol solution of the mixture. X-ray diffraction analysis confirmed the proposed structure under the exclusive tautomeric form **6a** in the crystal state (C13–N3≈1.36 Å>C1–N2≈1.33 Å: Fig. 2), thus suggesting a significant mesomeric contribution of the form **A** for the parent chloroisoindole **3**.

Prior to an attempt at metal-halogen exchange of the C–Cl bond of **3**, protection of the carbaldehyde group was first envisaged by acid-catalyzed formation of an acetal using 2,2-dimethylpropane-1,3-diol in toluene at room temperature (Scheme 3). These conditions indeed resulted in the protection of the aldehyde function, but induced concomitant hydrolysis of the C–Cl bond, thus giving the isoindolinone **7a** in 65% yield. The formation of the amide function was clearly evidenced by the appearance of an intense C=O stretching vibration band at 1687 cm^{-1} in the IR spectrum of **7a**, and by a mass spectrum (MS), which isotopic patterns corresponded to a non-chlorinated product. Attempts at acidic hydrolysis of **7a** (using either PTSA or HCl) failed to generate the non-conjugated aldehyde **7b**, while **7a** was recovered unreacted.

Acetalization of **3** was then attempted under 'neutral' conditions by treatment with triethyl orthoformate in refluxing ethanol (Scheme 4). Two products were formed in almost equal amounts, which, after separation by chromatography, were respectively attributed to the acetal **8** and the enolic ether derivative **9**. Both of

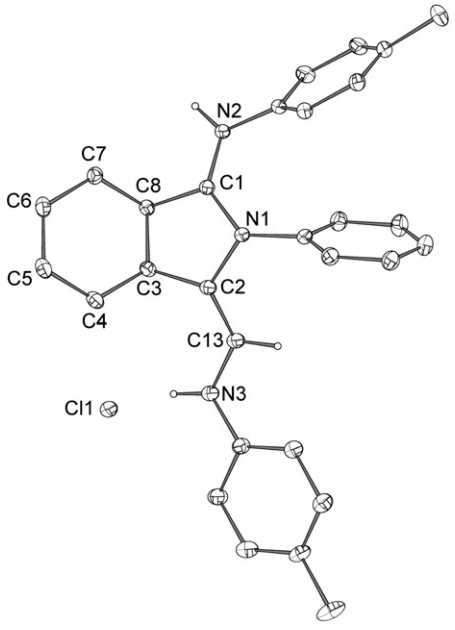
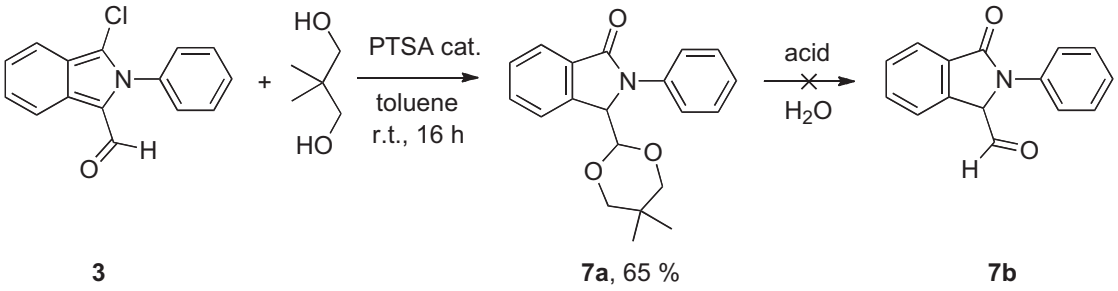
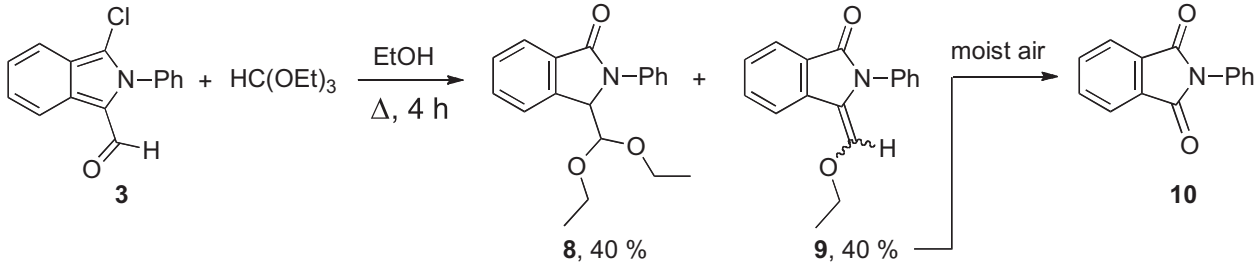


Fig. 2. Cameron diagram of the X-ray crystal structure of **6a** (Scheme 2). *R*=5.5%. Selected bond lengths in Å: C1–N1: 1.3499(11), C2–N1: 1.4381(12), C1–C8: 1.4514(12), C2–C3: 1.4420(13), C3–C4: 1.4020(13), C4–C5: 1.3880(16), C5–C6: 1.4036(16), C6–C7: 1.3883(13), C7–C8: 1.3981(13), C1–N2: 1.3280(11), C2–C13: 1.3663(13), C13–N3: 1.3575(13). Selected bond angles in degrees: C1–N2–C19: 128.50(8), C2–C13–N3: 126.51(10), N1–C1–N2: 128.11(8), C13–C2–N1: 119.69(9).



3 **7a**, 65 % **7b**

Scheme 3. Acid-catalyzed acetalization of the carbaldehyde function of **3**, with concomitant hydrolysis of the C–Cl bond.



3 **8**, 40 % **9**, 40 % **10**

Scheme 4. Reactivity of **3** with triethyl orthoformate under 'neutral' conditions.

them proved to contain the amide function again (as indicated by strong IR absorption bands at 1697 cm^{-1}), thus confirming the high sensitivity of the C–Cl bond, even under non- or weakly acidic conditions. The enol ether **9** was obtained as a mixture of *Z* and *E* isomers in a 3/1 ratio (without assignment). This product proved sensitive to oxidation and/or hydrolysis, giving *N*-phenylphthalimide **10** after being kept under air for a few days at room temperature (the structure of **10** was confirmed by X-ray diffraction analysis of a single crystal).[7]

Attempts at reducing the carbaldehyde function of **3** by various methods ($NaBH_4$/MeOH, $LiAlH_4$/THF, Canizzaro conditions in the presence of paraformaldehyde) afforded intractable mixtures, which attempted partial analyses were not conclusive. Irreversible masking of the carbaldehyde group of **3** was finally attempted by Wittig reaction with methylenetriphenylphosphorane, but the expected alkene could not be isolated from the reaction mixture. Although the ^{1}H NMR spectrum of the crude mixture gave evidence for the formation of an ethenyl moiety, MS analysis clearly indicated that the chlorine atom was removed.

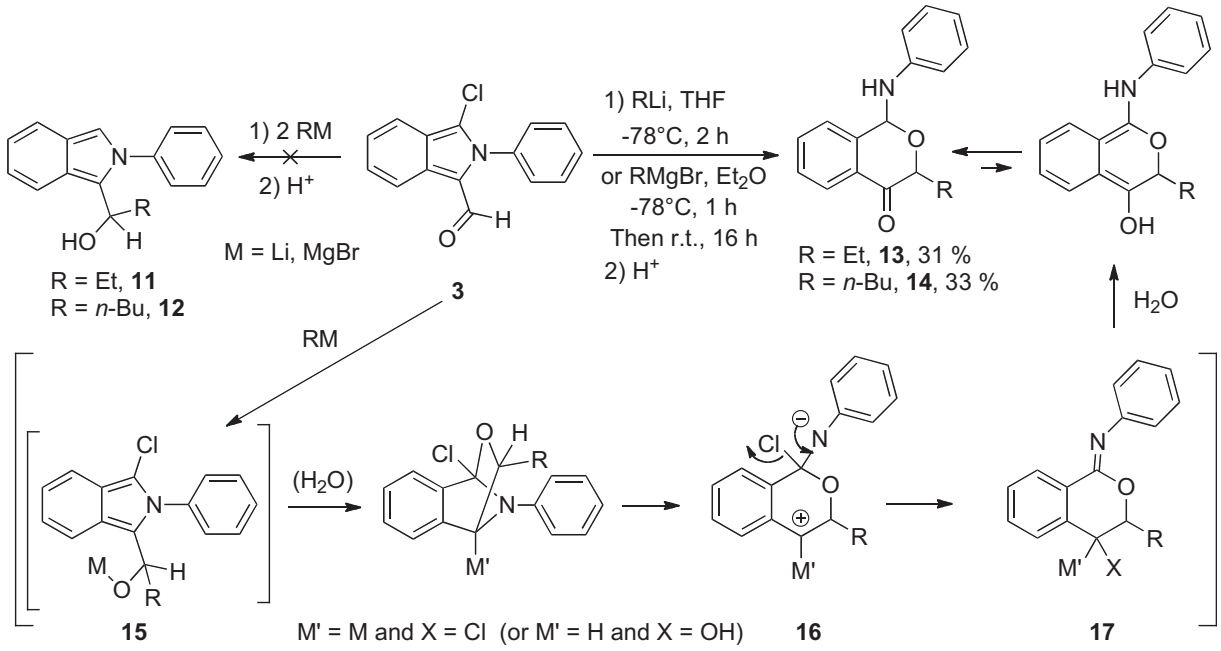
Facing the high sensitivity of the C–Cl bond of **3** in either acidic or 'neutral' protic medium (acetalization reactions can indeed not be performed under strictly basic conditions), metallation of the chlorinated carbon atom was finally investigated without preliminary protection of the carbaldehyde group. Inspired by a recent report by L. Jiao et al. dealing with the reactivity of benzo-fused BODIPYs bearing a chlorine atom at the equivalent 3-position of the isoindole motif,[8] a Pd(II)/Cu(I)-mediated Sonogashira coupling between the 3-chloro-isoindole **3** and tri-(isopropyl)silylacetylene in the presence of a base (triethylamine or potassium carbonate) was first attempted in THF and toluene solutions, but no coupling product could be detected and the starting material **3** was recovered in each case. Under more daring conditions, direct treatment of **3** with magnesium turnings in THF also proved non-productive, even after activation with I_2, mainly affording the unreacted starting material.

Finally, in an attempt at performing addition to the carbaldehyde group and metal-chlorine exchange in one pot, 2 equiv of ethylmagnesium bromide or butyllithium were added to a solution of **3** at −78 °C. After hydrolysis, the expected C-3-unsubstituted products **11** and **12** were not obtained. Instead, the unexpected 4-isochromanones **13** and **14** were observed as major products in the ^{1}H NMR spectra of the crude materials (in ca. 75–80 % estimated crude yields). Their purification proved quite problematic, but allowed **13** and **14** to be isolated in ca. 30% yield as 2/1 mixtures of diastereoisomers (Scheme 5).

As, in principle, the generation of **13** and **14** requires a single equivalent of alkylmetal reagents only, a mechanistic rationale is proposed in Scheme 5. It first involves the addition of the alkylmetal to the carbaldehyde, thus generating the alkoxide adduct **15**, which, in the absence of water molecule, might attack the chlorinated C-3 atom. The driving force of this process could be attributed to the aromatization of the benzoquinodimethane ring. The resulting fused pyrrolidine ring would then be opened by cleavage of the C–N bond with concomitant formation of a benzylic metalcarbenium centre and stabilization of the negative charge at the nitrogen atom of the anilide **16**. Elimination of the chloride ion would then give a carbenoid-iminoester **17** (M′=M, X=Cl), which upon hydrolysis would afford the 1-amino-4-isochromanones **13** and **14** (Scheme 5). Alternatively, invokation of the carbenoid intermediate might be avoided by considering that the primary alkoxide **15** would be stable in solution until the hydrolytic treatment, and that the rearrangement would be lately induced by a water molecule, through a benzylic carbenium intermediate **16** (M′=H) and a benzylic alcohol **17** (M′=H, X=OH).

The structure of **14** was confirmed by X-ray diffraction analysis of crystals deposited by slow evaporation of a 1/1 Et_2O/CH_2Cl_2 solution at room temperature (Fig. 3). Only the isomer bearing the butyl and the anilinyl substituents in *trans* position crystallized, whereas both isomers were present in solution, as indicated by the presence of two multiplets for the C-2–H signals at 4.32 and 4.43 ppm in the ^{1}H NMR spectrum of **14**.

Among the known functional 4-isochromanones (1*H*-2-benzopyran-4(3*H*)-ones), most of them are oxygenated at the C-1 position, in particular in the tricyclic series,[9] where 1-amino,1-oxy derivatives have also been described.[10] Representatives with hydrogenated C-1 positions (i.e., with a CH–OR vertex) are



Scheme 5. Reaction of **3** with organolithium and organomagnesium nucleophiles, and proposed mechanism for the rearrangement of the isoindole core of **3** to the 4-isochromanone core of **13** and **14**.

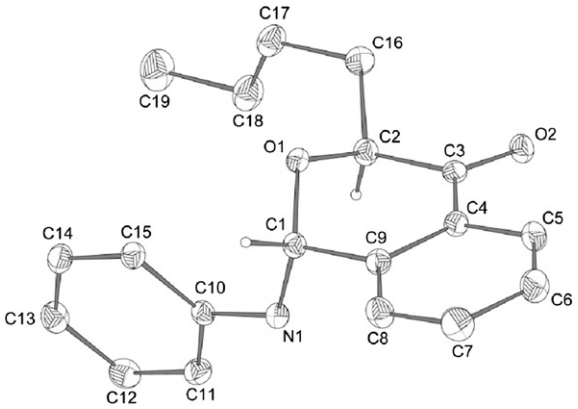


Fig. 3. Cameron diagram of the X-ray crystal structure of the *trans*-1-phenylamino-1*H*-2-benzopyran-4(3*H*)-one *trans*-**14** (Scheme 5). *R*=4.4%. Selected bond lengths in Å: C_1-O_1: 1.4329(10), O_1-C_2: 1.4289(10), C_2-C_3: 1.5186(12), C_3-O_2: 1.2243(10), C_3-C_4: 1.4775(12), C_4-C_9: 1.4007(12), C_1-C_9: 1.5084(12), C_1-N_1: 1.4380(11). Selected angles in degrees: $C_1-O_1-C_2$: 113.40(6), $O_1-C_1-N_1$: 114.09(7), $O_1-C_1-C_9$: 109.40(6), $O_2-C_3-C_4$: 122.26(8), $O_2-C_3-C_2$: 120.13(8).

exemplified,[11] but to the best of our knowledge, **13** and **14** (with a CH–NHPh C-1 vertex) are the first examples of 1-amino representatives.

3. Conclusion

The peculiar electrophilic character of the 3-chloro-2-phenylisoindole-1-carbaldehyde **3** can be related with π-electron-richness and reactivity of the isoindole core. The high sensitivity of the C–Cl bond, which was systematically cleaved whatever the experimental conditions used is however key for the unprecedented rearrangement of the isoindole core to the isochromanone core induced by nucleophilic addition of alkylmetals to the carbaldehyde group of **3**. Generalization of this reactivity would allow the investigation of chemical and biological properties of 1-amino-4-isochromanones.

4. Experimental section

4.1. General

THF and diethylether were dried and distilled over sodium/benzophenone, pentane and dichloromethane over P_2O_5. All other reagents were used as commercially available. In particular, commercial solutions of *n*-BuLi were 2.5 M in hexane and EtMgBr were 3 M in diethylether. All reactions were carried out under nitrogen or Argon using Schlenk and vacuum line techniques. Column chromatography was carried out on silicagel (60 P, 70–200 mm). Silica gel thin-layer chromatography plates (60F254, 0.25 mm) were revealed under UV. The following analytical instruments were used. ^{1}H and ^{13}C NMR: Bruker DPX 300, Avance 300 or Avance 400 spectrometers. Mass spectrometry: Quadrupolar Nermag R10-10H spectrometer. NMR chemical shifts δ are in parts per million, with positive values to high frequency relative to the tetramethylsilane reference; coupling constants *J* are in Hertz. IR: 0.1 mm CaF_2 cell, Perkin–Elmer GX FTIR. Absorption spectra: Perkin–Elmer UV–vis Win-Lab Lambda 35. Emission spectra: FluoroMax-4 Spectrofluorometer HoribaJobinYvon.

4.2. Crystallographic data and structural refinement parameters for compounds 6 and 14

Intensity data for compound **14** were collected on an Agilent Gemini diffractometer using a Cu Kα radiation source. Data for **6** were collected on a Bruker Apex2 diffractometer using a graphite-monochromated Mo Kα radiation source. Structures were solved by direct methods using SIR92,[12] or SHELXS,[13] and refined by full-matrix least-squares procedures on F using the programs of the PC version of CRYSTALS.[14] For compound **14**, a non-merohedral twin (0.93/0.07) was detected. Data were treated using the Crysalis^{Pro} program,[15] and permitted to improve the final results. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[16] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using a riding model. CCDC-862026 and 862027 contain 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.

	6	14
Chemical formula	$C_{29}H_{26}ClN_3$	$C_{19}H_{21}NO_2$
M (g mol^{-1})	452.00	295.38
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
a (Å)	10.4531(5)	8.8753(4)
b (Å)	10.6908(5)	10.0547(4)
c (Å)	11.1744(5)	10.6142(4)
α (°)	96.211(2)	64.768(3)
β (°)	103.656(2)	67.583(4)
γ (°)	97.933(2)	79.728(3)
V (Å^3)	1188.92(10)	791.94(6)
Z	2	2
ρ_{calcd}	1.263	1.239
μ (mm^{-1})	0.183	0.632
Θ_{max} (°)	34.75	60.63
Crystal size (mm)	0.20×0.20×0.30	0.20×0.20×0.25
λ (Å)	0.71073 (MoK$_\alpha$)	1.54180 (CuK$_\alpha$)
Scan mode	Φ and Ω scans	Φ and Ω scans
T(K)	180	180
Refl. measured	58,484	4795
Refl. unique	9703	2372
R_{int}	0.019	0.026
Refl. with $I>3\sigma(I)$	8411	4126
Nb. parameters	298	200
R	0.0521	0.0444
Rw	0.0565	0.0305
Residual electron density (ē Å^{-3})	−0.33/0.88	−0.26/0.21

4.3. Synthesis procedures

4.3.1. 3-Chloro-2-phenyl-2H-isoindole-1-carbaldehyde ***3***. $POCl_3$ (1.53 g, 10 mmol) was added dropwise to DMF (0.73 g, 10 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. After cooling down the solution back to 0 °C, a suspension of 1-phenylisoindolinone **4** (0.7 g, 3.3 mmol) in DMF (2 mL) was added. Subsequently, the reaction mixture was heated at 80 °C for 6 h. Then, after cooling to room temperature, chloroform (10 mL) and ice were added. The organic layer was collected and the chloroform was removed under reduced pressure. Then, KOH (4 M, 5 mL) and MeOH (5 mL) were added to the crude residue, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered, washed with water, and recrystallized from *i*-PrOH, to give **3** as a light yellow solid (0.58 g, 69%). Mp=98–99 °C. IR (ATR): $\nu_{C=O}$=1614 cm^{-1} ^{1}H NMR (acetone-d^6): δ=7.36 (t, J=7.8 Hz, 1H, *H*-5), 7.49 (t, J=7.8 Hz, 1H, *H*-6), 7.72 (m, 6H, *H*-4, N–Ph), 8.33 (d, J=7.8 Hz, 1H, *H*-7), 9.46 (s, 1H, C*H*O). ^{13}C{^{1}H} NMR (acetone-d^6): δ=118.6, 120.5, 122.2, 124.4, 128.2, 128.4, 129.4, 130.2, 135.3, 176.1. UV–vis: λ_{max} ($CHCl_3$): 379 nm (ε=22,060 L mol^{-1} cm^{-1}). Fluo (λ_{ex}=379 nm): λ_{Em}=409 nm. MS (DCI/NH_3): m/z=256.0 $[MH]^+$. HRMS (DCI/CH_4): m/z calcd for $C_{15}H_{11}NOCl$: 256.0529; found: 256.0529.

4.3.2. N-(4-methylphenyl)-3-{[(4-methylphenyl)amino]methylidene}-2-phenyl-2,3-dihydro-1H-isoindol-1-imine hydrochloride ***6a***. A solution of **3** (255 mg, 1 mmol) and 4-methylaniline (107 mg, 1 mmol) in MeOH (5 mL) was stirred at room temperature for 24 h. The resulting precipitate was filtered and washed with MeOH (3×1 mL) to give **6a** as a yellow solid (115 mg, 51%). ^{1}H NMR (CD_3OD): δ=2.28 (s, 3H, Me), 2.44 (s, 3H, Me), 6.86 (s, 1H, C=C*H*), 6.95 (d, J=8.0 Hz, 2H, N$^+$-*o*-Ar), 7.13 (m, 3H, C=N-*m*-Ar, N-*p*-Ph), 7.29–7.35 (m, 5H, –C=N-*o*-Ar, N$^+$-*m*-Ar), (1H, *H*-5), 7.66–7.88 (m, 6H, N-*o*, *m*-Ph, *H*-4, *H*-6), 8.42 (d, J=8.0 Hz, 1H, H-7). ^{13}C{^{1}H} NMR (CD_3OD): δ=19.3, 19.7, 116.3, 121.2, 121.3, 124.4, 126.1, 126.6(2c), 126.8(2c), 128.8(2c), 129.8(2c), 130.0(2c), 130.5(2c), 130.9, 131.4, 132.5, 132.8, 133.1, 133.3, 133.8, 138.6, 139.0, 151.8. UV–vis: λ_{max} (MeOH): 432 nm (ε=38,904 L mol^{-1} cm^{-1}). Fluo (λ_{ex}=432 nm): λ_{Em}=497 nm. MS (ESI>0): m/z 416.21 $[M]^+$; HRMS (ESI>0): m/z calcd for $C_{29}H_{26}N_3$: 416.2127; found: 416.2119.

4.3.3. 3-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-phenyl-2,3-dihydro-1H-isoindol-1-one ***7a***. A mixture of **3** (255 mg, 1 mmol), 2,2-dimethylpropane-1,3-diol (105 mg, 1 mmol), and PTSA (40 mg, 0.2 mmol) in toluene (5 mL) was stirred for 16 h at rt. After cooling, the solvent was removed under reduced pressure. The crude product was purified by silicagel chromatography (pentane/EtOAc 6/4, v/v) to give **7a** as a white powder (210 mg, 65%). R_f (heptane/EtOAc 1/1, v/v)=0.37. Mp=168 °C. IR (ATR): $\nu_{C=O}$=1687 cm^{-1} ^{1}H NMR ($CDCl_3$): δ=0.63 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 3.17 (d, J=11.2 Hz, 1H, CH_2), 3.39 (d, J=11.2 Hz, 2H, CH_2), 3.68 (d, J=11.2 Hz, 1H, CH_2), 4.74 (d, J=2.1 Hz, 1H, C*H*(O)$_2$), 5.27 (d, J=2.1 Hz, 1H, C*H*–N), 7.24 (t, J=7.6 Hz, 1H, *p*-N–Ph), 7.52 (m, 6H, *o*-,*m*-N–Ph, *H*-5, *H*-6), 7.83 (d, J=7.6 Hz, 1H, *H*-4), 7.92 (d, J=7.6 Hz, 1H, *H*-7). ^{13}C{^{1}H} NMR ($CDCl_3$): δ=21.5, 22.9, 30.3, 63.2, 76.5, 77.6, 98.6, 123.7, 124.1, 124.6, 125.8, 128.6, 129.1, 131.6, 132.9, 137.5, 141.1, 167.8. MS (DCI/NH_3): m/z=324.1 $[MH]^+$, 341.1 $[M+NH_4]^+$. Elemental anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; found: C, 74.38; H, 6.52; N, 4.32.

4.3.4. 3-(Diethoxymethyl)-2-phenyl-2,3-dihydro-1H-isoindol-1-one ***8***. A mixture of **3** (255 mg, 1 mmol), triethyl orthoformate (225 mg, 1.5 mmol), in EtOH (5 mL) was refluxed for 4 h. After cooling to room temperature, ethanol was removed under reduced pressure. The crude product was purified by silicagel chromatography (pentane/EtOAc 6/4, v/v) to give **8** as a yellow powder (0.125 g, 40%). R_f (heptane/EtOAc 1/1, v/v)=0.4. Mp=70–71 °C. IR (ATR): $\nu_{C=O}$=1697 cm^{-1} ^{1}H NMR ($CDCl_3$): δ=1.03 (t, J=6.9 Hz, 3H, CH_3), 1.22 (t, J=6.9 Hz, 3H, CH_3), 3.30 (dq, J=7.0 Hz, J=2.0 Hz, 1H, CH_2), 3.43 (dq, J=7.0 Hz, J=2.0 Hz, 1H, CH_2), 3.56 (dq, J=7.0 Hz, J=2.0 Hz, 1H, CH_2), 3.69 (dq, J=7.0 Hz, J=2.0 Hz, 1H, CH_2), 4.58 (d, J=4.0 Hz, 1H, C*H*(O)$_2$), 5.32 (d, J=4.0 Hz, 1H, C*H*–N), 7.26 (t, J=7.5 Hz, 1H, *p*-N–Ph), 7.57 (m, 6H, *o*-,*m*-N–Ph, *H*-5, *H*-6), 7.79 (d, J=7.5 Hz, 1H, *H*-4), 7.92 (d, J=7.5 Hz, 1H, *H*-7). ^{13}C{^{1}H} NMR ($CDCl_3$): δ=15.0, 15.3, 63.4, 64.6, 65.6, 102.7, 123.5, 123.7, 124.8, 125.4, 128.6, 129.0, 131.8, 132.8, 137.9, 168.0. MS (DCI/NH_3): m/z=312.1 $[MH]^+$, 329.1 $[M+NH_4]^+$. Elemental anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50; found: C, 73.15; H, 6.57; N, 4.57.

4.3.5. 3-(Ethoxymethylidene)-2-phenyl-2,3-dihydro-1H-isoindol-1-one ***9***. The product **9** was isolated by purification on silicagel of the reaction mixture obtained in the preparation of **8**. R_f (heptane/EtOAc 1/1, v/v)=0.32. Mp=136–140 °C. IR (ATR): $\nu_{C=O}$=1697 cm^{-1} ^{1}H NMR ($CDCl_3$): δ=1.07, 1.14 (2t, J=6.9 Hz, 3H, CH_3), 3.85, 4.00 (2q, J=6.9 Hz, 2H, CH_2), 6.37, 6.63 (2s, 1H,=C*H*), 7.45–8.09 (m, 9H, *o*-,*m*-,*p*-N–Ph, *H*-4, *H*-5, *H*-6, H-7).^{13}C{^{1}H} NMR ($CDCl_3$): δ=14.7, 59.2, 123.3, 123.7, 124.7, 126.6, 128.1, 129.1, 129.3, 131.7, 132.7, 134.4, 136.1, 137.7, 167.3. MS (DCI/NH_3): m/z=266.1 $[MH]^+$.

4.3.6. 3-Ethyl-1-(phenylamino)-3,4-dihydro-1H-2-benzopyran-4-one ***13***. A EtMgBr solution (0.13 mL, 1 mmol) was added dropwise to a solution of **3** (255 mg, 1 mmol) in diethylether (15 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, and then for 16 h at rt. The mixture was then hydrolyzed with saturated aqueous NH_4Cl, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by silicagel chromatography (pentane/EtOAc 6/4, v/v) to give **13** as a brown solid (94 mg, 35%). R_f (heptane/EtOAc 1/1, v/v)=0.31. Mp=92–93 °C. IR (ATR): ν_{N-H}=3372, $\nu_{C=O}$=1697 cm^{-1} ^{1}H NMR ($CDCl_3$): δ=1.00, 1.09 (2t, J=7.5 Hz, 3H, CH_3), 1.86–2.22 (m, 2H, CH_2), 4.25, 4.45 (2m, 1H, C*H*(C=O)), 4.59, 4.62 (2m, 1H, N*H*), 6.22 (m, 1H, C*H*–N), 6.88–6.98 (m, 3H, *o*-,*p*-

N–Ph), 7.26–7.65 (m, 5H, *m*-N–Ph, *H*-5, *H*-6, *H*-7), 8.07 (m, 1H, *H*-8). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ=9.7, 23.4, 74.5, 80.4, 114.1, 114.9, 119.6, 123.6, 124.6, 129.3, 131.0, 134.1, 141.2, 145.6, 196.7. MS (DCI/NH_3): *m*/*z*=268.1 $[MH]^+$. HRMS (DCI/CH_4): *m*/*z* calcd for $C_{17}H_{18}NO_2$ $[MH]^+$: 268.1338; found: 268.1340.

4.3.7. 3-Butyl-1-(phenylamino)-3,4-dihydro-1H-2-benzopyran-4-one ***14***. A *n*-BuLi solution (0.4 mL, 1 mmol) was added dropwise to the solution of **3** (255 mg, 1 mmol) in THF (15 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, and then, the mixture was hydrolyzed with saturated aqueous NH_4Cl, washed with brine, and dried over anhydrous $MgSO_4$. Then, the solvent was removed under vacuum. The crude product was purified by silica-gel chromatography (pentane/EtOAc 6/4, *v*/*v*) to give **14** as a brown solid (109 mg, 37%). R_f (heptane/EtOAc 1/1, *v*/*v*)=0.38. Mp=88–89 °C. IR (ATR): ν_{N-H}=3374, $\nu_{C=O}$=1682 cm^{-1} ^1H NMR ($CDCl_3$): δ=0.90 (m, 3H, CH_3), 1.29–2.07 (m, 6H, 3×CH_2), 4.32, 4.43 (2m, 1H, C*H*(C=O)), 4.65 (m, 1H, N*H*), 6.21 (m, 1H, C*H*–N), 6.90–6.97 (m, 3H, *o*-,*p*-N–Ph), 7.25–7.77 (m, 5H, *m*-N–Ph, *H*-5, *H*-6, *H*-7), 8.06 (m, 1H, *H*-8). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ=13.9, 22.4, 27.4, 29.7, 73.3, 81.6, 114.1, 114.9, 119.6, 126.5, 127.0, 129.3, 134.2, 141.2, 144.9, 145.6. MS (DCI/NH_3): *m*/*z*=296.1 $[MH]^+$. HRMS (DCI/CH_4): *m*/*z* calcd for $C_{19}H_{22}NO_2$: 296.1651; found: 296.1656.

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