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REACTION OF 1-ACYL AND AROYL-2-HYDROXY-3,3-DIMETHYL-INDOLINES WITH ARYLAMINES CATALYZED BY BF_3·ETHERATE. FORMATION OF DIHYDROINDOLO[1,2-*c*]QUINAZOLINE

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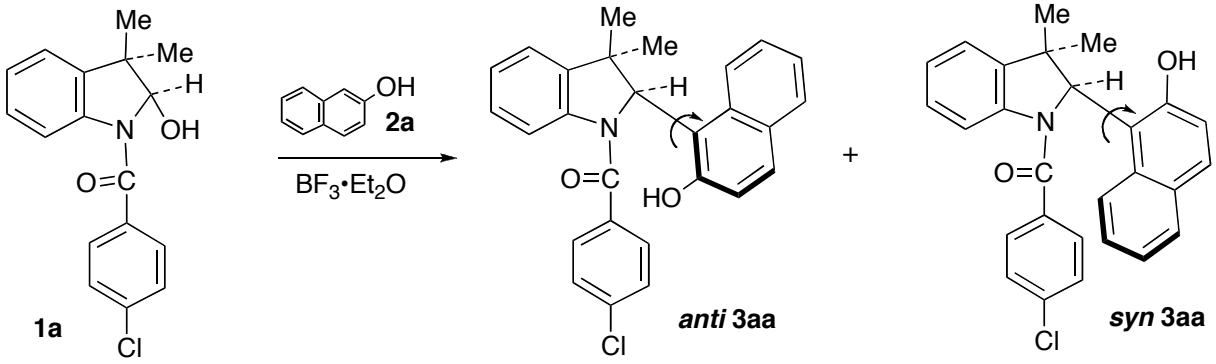
Abstract – The reaction of (4-chlorophenyl)(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)methanone or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone with 2-aminonaphthalene in the presence of excess amounts of BF_3·Et_2O gave the 14,14-dimethyl-14,14a-dihydrobenzo[*f*]indolo[1,2-*c*]-quinazoline derivatives which are derived from the dehydrative cyclization of the coupling reaction product [2-(2-aminonaphthalen-1-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-chlorophenyl)methanone or 1-[2-(2-aminonaphthalen-1-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl]ethanone. The reactions of several (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)(substituted-phenyl)methanones or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone with *m*-anisidine gave the cyclization products together with the coupling reaction products. The structure of the cyclization product and the reaction mechanism are discussed based on the crystallographic and molecular orbital (MO) calculation data.

INTRODUCTION

In the previous papers,[1] we reported a simple method for synthesis of 2-aryl substituted indoline derivatives based on condensation of (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)(substituted-phenyl)methanones or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone with various electron-rich aromatic compounds in the presence of boron trifluoride-diethyl ether (BF_3·Et_2O).[1c] The reaction proceeds under very mild reaction conditions and provides a very important method for synthesis of isolable diastereomeric atropisomers arising from restricted rotation around a Csp^3-Csp^2 bond.

Molecular modeling study of the restricted rotation about the Csp^3-Csp^2 bond indicates that there are various interaction such as face-to-face interaction, edge-to-face interaction, C-H··O type hydrogen bonding interaction, coulomb-coulomb interaction and H··H short contacts.[2,3] During the restricted rotations around the C2-Ar, CO-Ar and >N-CO- bonds, the hydroxy oxygen atom is expected to approach to the amide carbonyl carbon within 2.4 Å, wherein the lone pair electron of the hydroxy oxygen may strongly interact with the positively charged carbonyl carbon.



Scheme 1

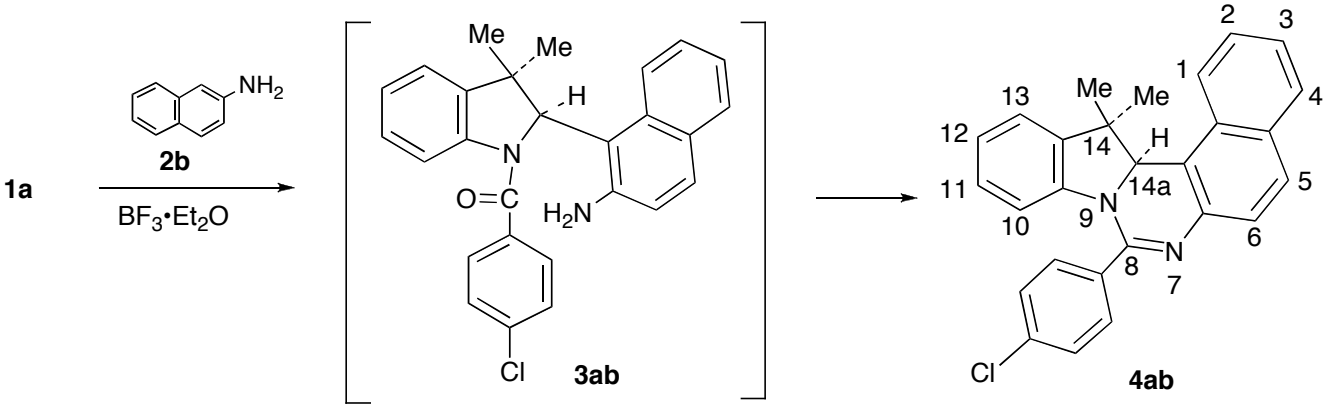
Based on this result, we supposed that the change of hydroxy group to amino group more strongly interacts with the carbonyl carbon to brake the rotation. The results are discussed here in detail based on the spectroscopic, crystallographic and molecular orbital (MO) calculation data.

RESULTS AND DISCUSSION

Heating of a mixture of (4-chlorophenyl)(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)methanone (**1a**), 2-aminonaphthalene (**2b**) (2.5 equiv., banned substance) and BF_3·Et_2O (5.0 equiv.) in dioxane at 60°C gave yellow crystals (**4ab**). The IR spectrum of **4ab** showed no carbonyl absorption band. The mass spectrum (MS) showed the molecular ion peak at 408 which is 18 smaller than that of the coupling reaction product, suggesting that the double dehydration reactions occurred during the reaction. The visible absorption spectrum exhibited a characteristic absorption band responsible for the presence of a long conjugated π-electron system. These data implied the formation of 8-(4-chlorophenyl)-14,14-dimethyl-14,14a-dihydrobenzo[*f*]indolo[1,2-*c*]quinazoline.

The dimethyl groups of the indoline moiety resonated at 1.14 and 1.61 ppm, whereas those of the coupling product **3ac** (derived from the reaction of **1a** with 1-aminonaphthalene (**2c**)) appeared at 0.75 and 1.54 ppm. Molecular modeling studies can explain the spectral behavior. The ring closure increases the spatial separation between the dimethyl groups and the naphthalene ring, resulting in a decrease in the ring current effect. The C14a-H hydrogen (>C*H*-naphthyl) appeared at 5.91 ppm as a

singlet. Interestingly, the ^{1}H-NMR spectrum of **4ab** showed the presence of high-field shifted aromatic hydrogens (6.27, 6.90 ppm) compared with those of the coupling product (**3ac**) (see Figure 1).



Scheme 2

To establish the stereostructure of the product, the single crystal X-ray analysis was undertaken. The computer-generated drawing of **4ab** is depicted in Figure 1.

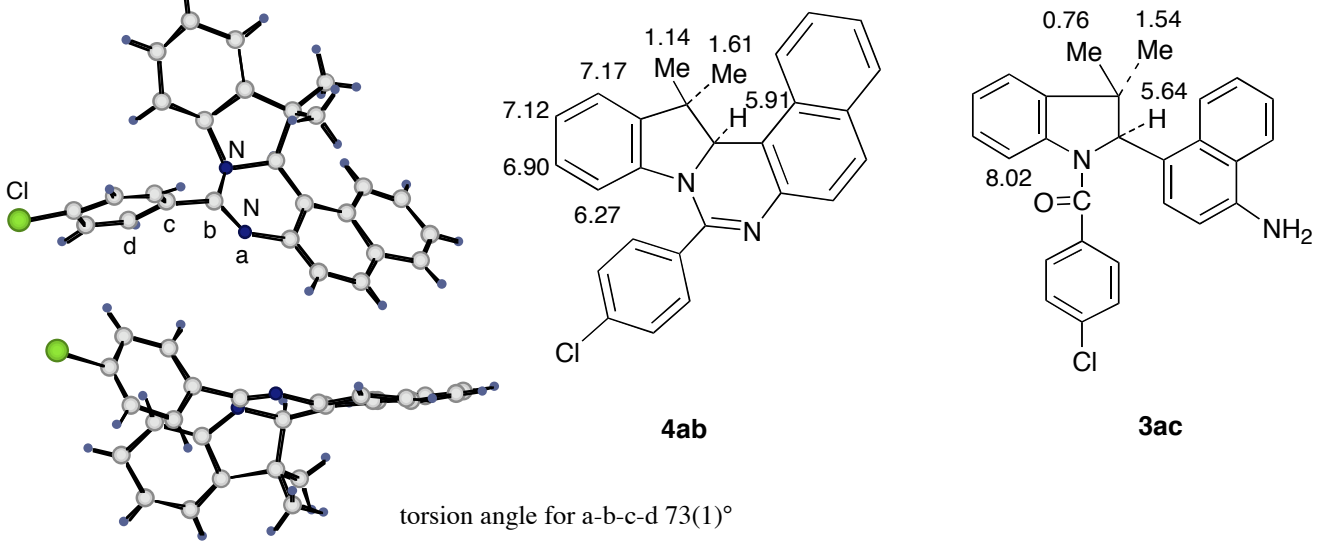


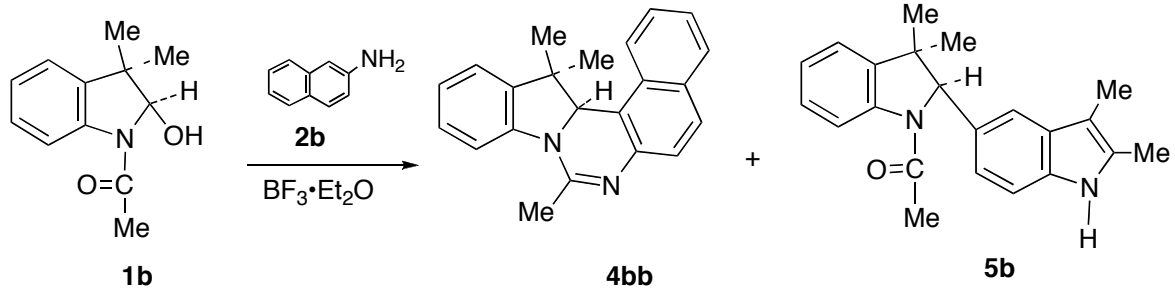
Figure 1. X-Ray Structure of **4ab** and ^{1}H-NMR Chemical Shifts of **4ab** and **3ac**.

As shown in Figure 1, there are two molecules of **4ab** in an asymmetric unit, which interact each other by edge-to-face interaction not only between the 4-chlorophenyl rings but also between the naphthyl rings. The pyrrolo[1,2-*c*]pyrimidine skeleton is *cis*-fused. Such the configuration forces the 4-chlorophenyl ring to take a perpendicular disposition with respect to the C=N double bond plane, leading to the tilted-T conformation between the 4-chlorophenyl and the indoline benzene rings. This structural feature also indicates that the C10-H proton of the indoline moiety is located *ca.* 2.4 Å above the plane of the

4-chlorophenyl ring. The AM1-optimized geometry[4] of **4ab** supports the X-ray structural feature, ruling out that the conformation of the 4-chlorophenyl ring is not arisen from the crystal packing forces, responsible for the high-field shift of the hydrogens of indoline benzene ring.

From these facts, it is obvious that the coupling reaction product (**3ab)** transformed to the cyclization product (**4ab**) by the action of the Lewis acid. In the reaction, the precursor (**3ab**) could not be detected.

The reaction of 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone (**1b**) with **2b** gave a similar product as yellow solid (**4bb**) together with a mixture of the 1-[2-(2,3-dimethylindol-5-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl]ethanone (**5b**). The two methyl groups of **4bb** resonate at 1.02 and 1.80 ppm. The high-field shift of the aromatic hydrogens of the indoline benzene ring was no longer observed.



Scheme 3

In order to know the reaction behavior toward aniline derivatives, we performed the reactions of (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)(4-nitrophenyl)methanone with various substituted anilines (**2d-k**).

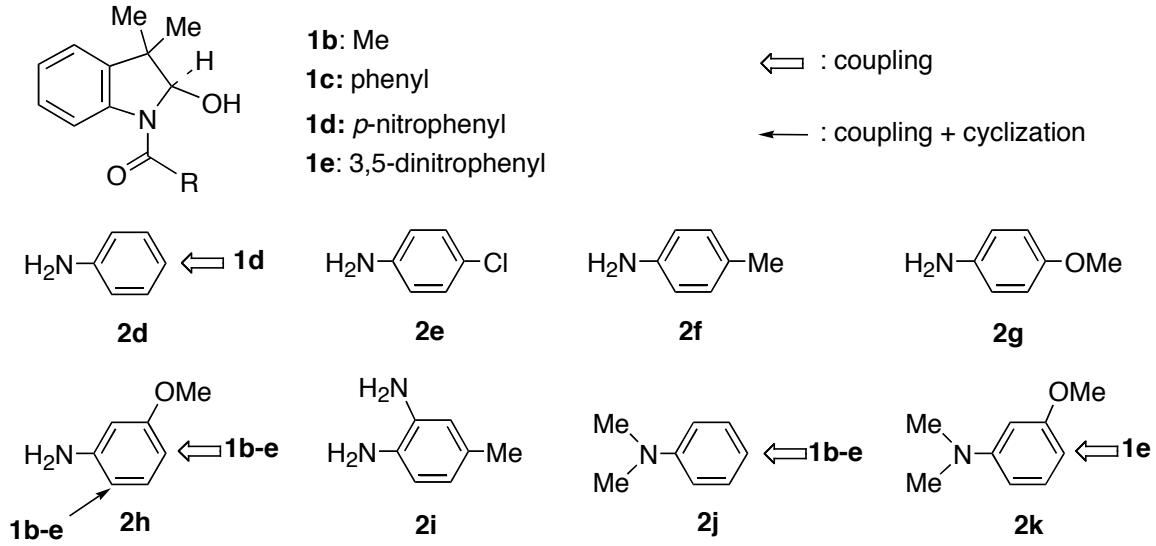
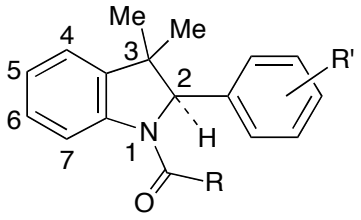
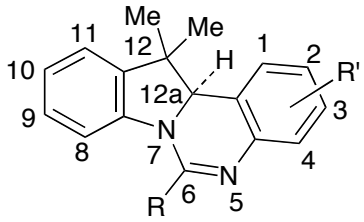


Chart 1



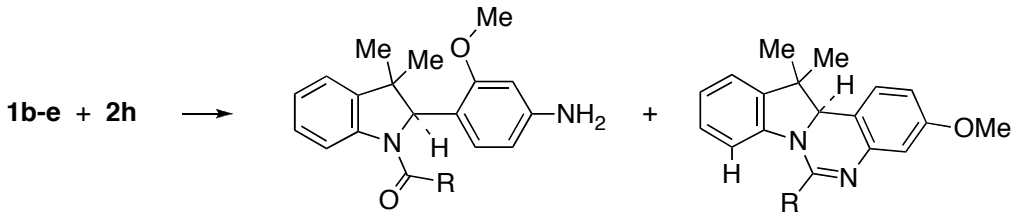
6xy

x: suffix of **1**
y: suffix of **2**



7xy

As the result, the coupling reactions were observed in aniline (**2d**), *m*-anisidine (**2h**), *N*,*N*-dimethylaniline (**2j**) and *N*,*N*-dimethyl-*m*-anisidine (**2k**). Of those, in the reactions with *m*-anisidine (**2h**), the coupling and cyclization reactions were observed according to the reaction site. The product ratios for the reactions of **1b-e** with **2h** are shown in Scheme 4. The structures of the products are determined by comparison of the ^{1}H-NMR spectra with those of **3ac**, **4ab** and **4bb**.

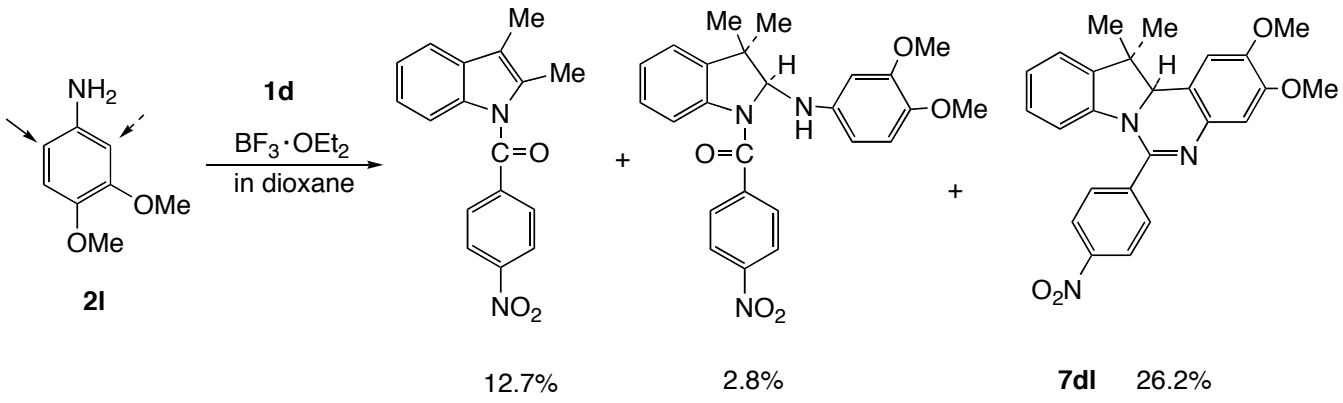


1b	R: Me	**6bh** (52)	**7bh** (15)
1c	phenyl	**6ch** (31)	**7ch** (30)
1d	*p*-nitrophenyl	**6dh** (46)	**7dh** (21)
1e	3,5-dinitrophenyl	**6eh** (31)	**7eh** (16)

Scheme 4

The main products are coupling reaction products at the 4-position. In the benzoyl derivative, the formation ratio is *ca*. 1:1. The ^{1}H-NMR spectra of **7ch**, **7dh** and **7eh** (R=aryl) showed considerably high-field shifted peaks of the aromatic hydrogens at 5.76-5.83 as seen in **4ab**, whereas the those of **7bh** (R=Me) appeared at 7.10-7.26 ppm.

In expectation of the improvement of the yield of the cyclization product, the reaction with 3,4-dimethoxyaniline (**2l**) was performed. However, the yield enhancement of the cyclization product (**7dl**) could not be observed but the Wagner-Meerwein type rearrangement product and the 2-anilinoindoline derivative were obtained.



Scheme 5

In the reaction of **1e** with **2h**, orange-colored crystals (**6eh**) were obtained. The UV-VIS absorption band continues beyond 480 nm, characteristic of charge-transfer (CT) absorption band. Comparison of the spectrum with that of a solution containing 3,5-dinitrobenzoic acid and *m*-anisidine indicates the presence of the intramolecular CT complexation.

The 4-nitrobenzoyl derivative (**6dh**) is yellow-colored crystal. Similar colorations were observed in **6dj** and **6ek** (see ref. 5a). The coloration is due to intramolecular charge-transfer (CT) interaction between donor (D) and acceptor (A) groups which are positioned in the vicinity of each other. The FMO of **6dj** supports this assumption, in which the HOMO localizes at 4-dimethylaminophenyl group whereas the LUMO localizes at 4-nitrophenyl group (Figure 2). The force of CT interaction between the aryl rings does not affect the stabilization of the atropisomers because the isomers could not be observed at room temperature. In crystalline state, the intermolecular donor-acceptor interactions can be observed between the 4-nitrophenyl and 4-dimethylaminophenyl rings (Figure 2 and ref. 5b).

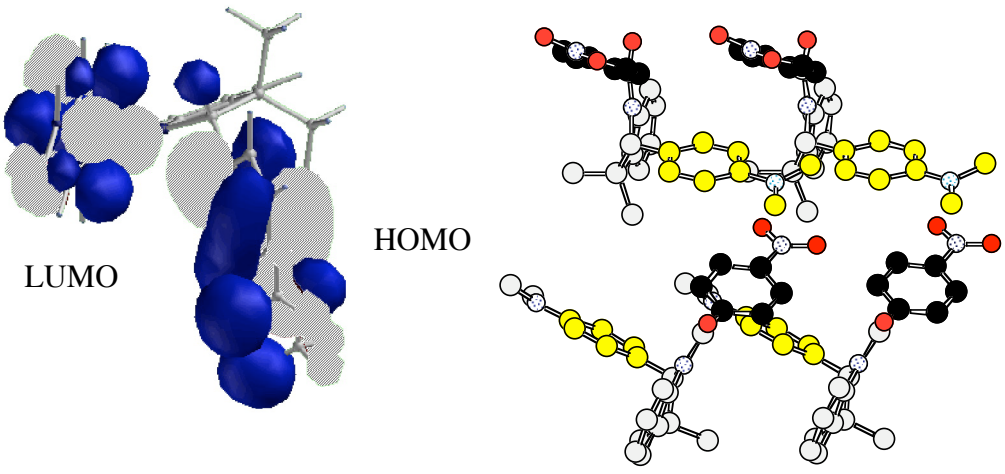


Figure 2. HOMO and LUMO Localized at the Benzoyl and Napthyl Rings in **6dj** and X-Ray Packing Structure of **6dj**.

To clarify the cyclization reaction mechanism, we carried out the molecular orbital calculations. The AM1 calculation of aniline and aniline-BF_3-complex indicates that the coordination of BF_3·Et_2O to the amino group does not affect not only on the HOMO coefficient in both the size and shape but also on the net charge. However, the HOMO energy level is lowered from -8.521 eV to -8.810 eV with the coordination of BF_3, unfavorable for the Friedel-Crafts reactivity. In *m*-anisidine, the HOMOs of *m*-anisidine and *m*-anisidine·BF_3 are -8.453 eV and -8.694 eV, respectively. Introduction of methoxy group compensates the decrease of the reactivity due to the BF_3 coordination.

As the atropisomers of **3ab** could not be isolated in the reaction of **1a** with **2b**, the possible structures of a pair of atropisomers (***syn-*** and ***anti-*****3ab**) were obtained from the density functional theory (DFT) calculations at the B3LYP/6-31G*[6] level using the whole structures without simplification. The calculations indicate that the ***anti*** atropisomer is 1.6 kcal/mol more stable than the ***syn*** atropisomer (2.8 kcal/mol in AM1), wherein the distance between the amino nitrogen and the amide carbon is 3.327 Å and the hydrogen bond distance between the amino hydrogen and the indoline nitrogen (net charge = -0.27) is 2.313 Å. These indicate that the *anti* isomer of **3ab** is predominant in the equilibration at the reaction temperature and its ground-state structure is very favorable for the ring closure (see Figure 3).

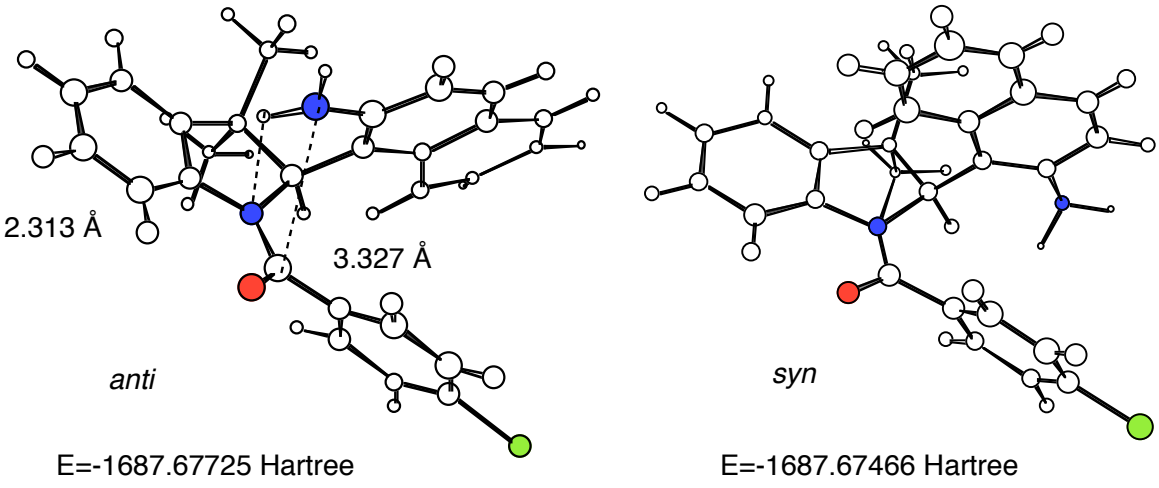


Figure 3. B3LYP/6-31G* Optimized Structures of Possible *anti* **3ab** and *syn* **3ab**.

Next, we calculated the AM1 transition structure (**TS**) for the ring closure using a model compound of protonated **3ab** (**3ab**-H^+) instead of the BF_3-complex. The structures of the starting material (**GS-1**), TS, intermediate (**IM**) and product (**GS-2**) are depicted in Figure 4.[7] These calculations indicate that a weak interaction exists between the amide carbonyl carbon and amino nitrogen (O=C··NH_2 3.369 Å) even in the **GS-1** and the creating bond distance in the **TS** is 1.908 Å. The reaction barrier is very low (16.3 kcal/mol), supporting the observed reactivity. The energetically unstable intermediate (**IM**) may be

converted to the final product (**GS-2**) with dehydration.

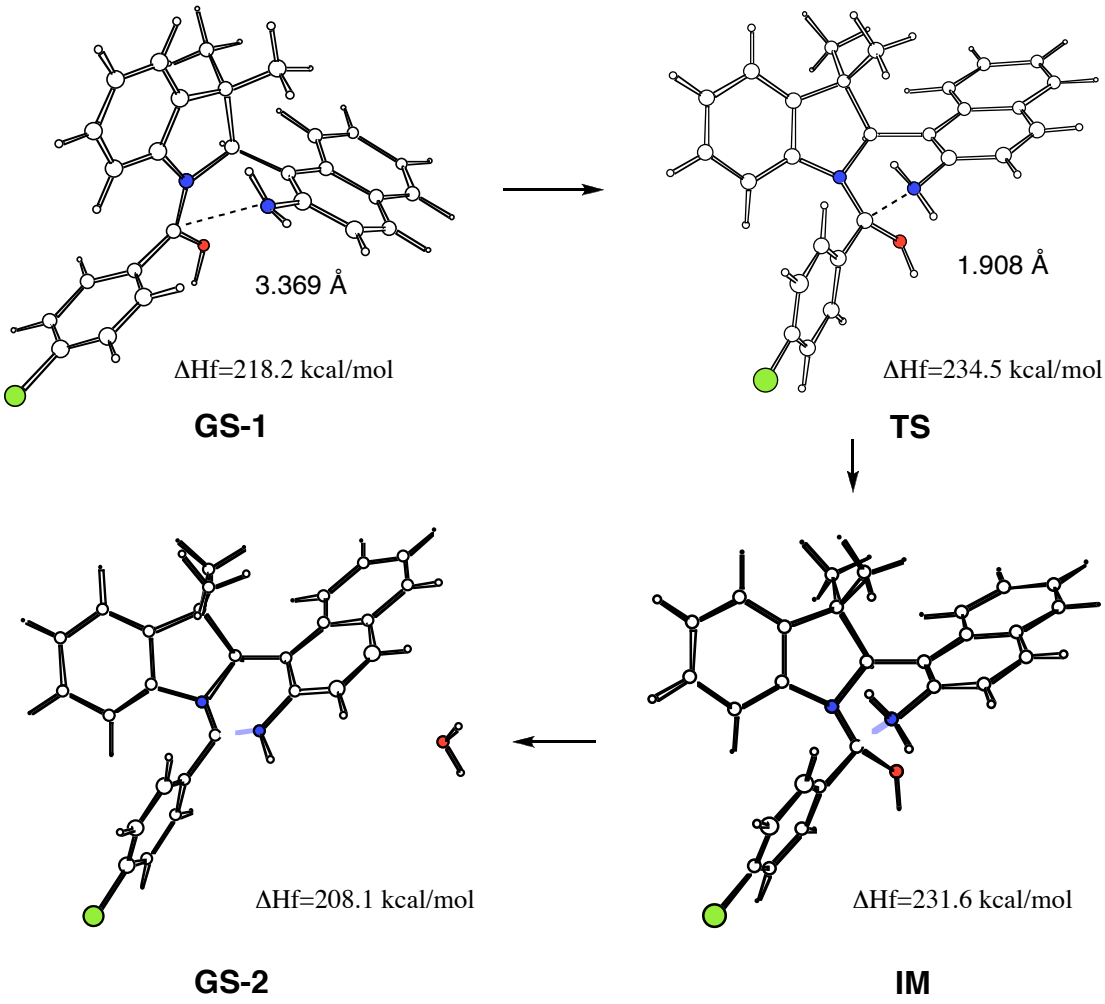
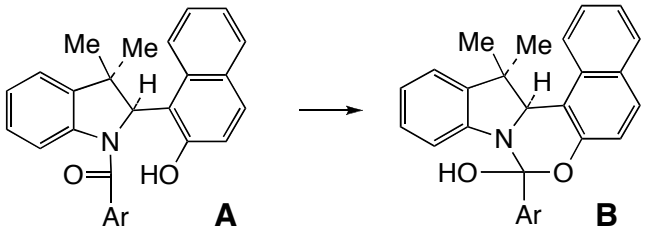
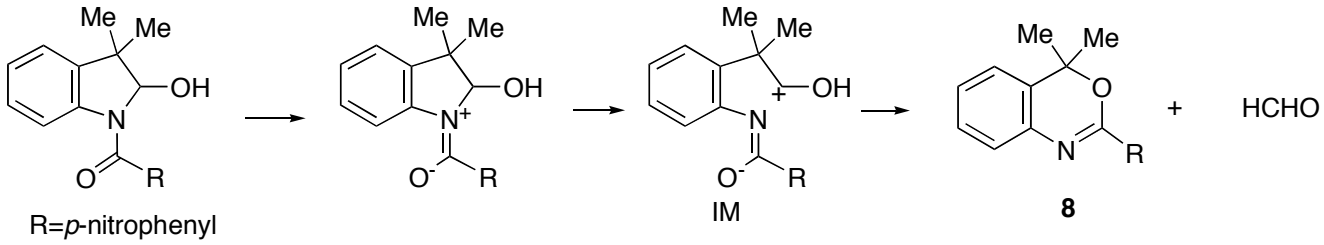


Figure 4. AM1 Transition structure for the ring closure of protonated **3ab** and related compounds.

In the reactions of **1** with 2-naphthol, a similar interaction leading to the ring closure may occur. However, the AM1 calculation of the reaction indicates that the reaction product (**B**) is less stable than the starting material (**A**), indicating that the absence of the successive dehydration reaction can not stabilize the reaction system.

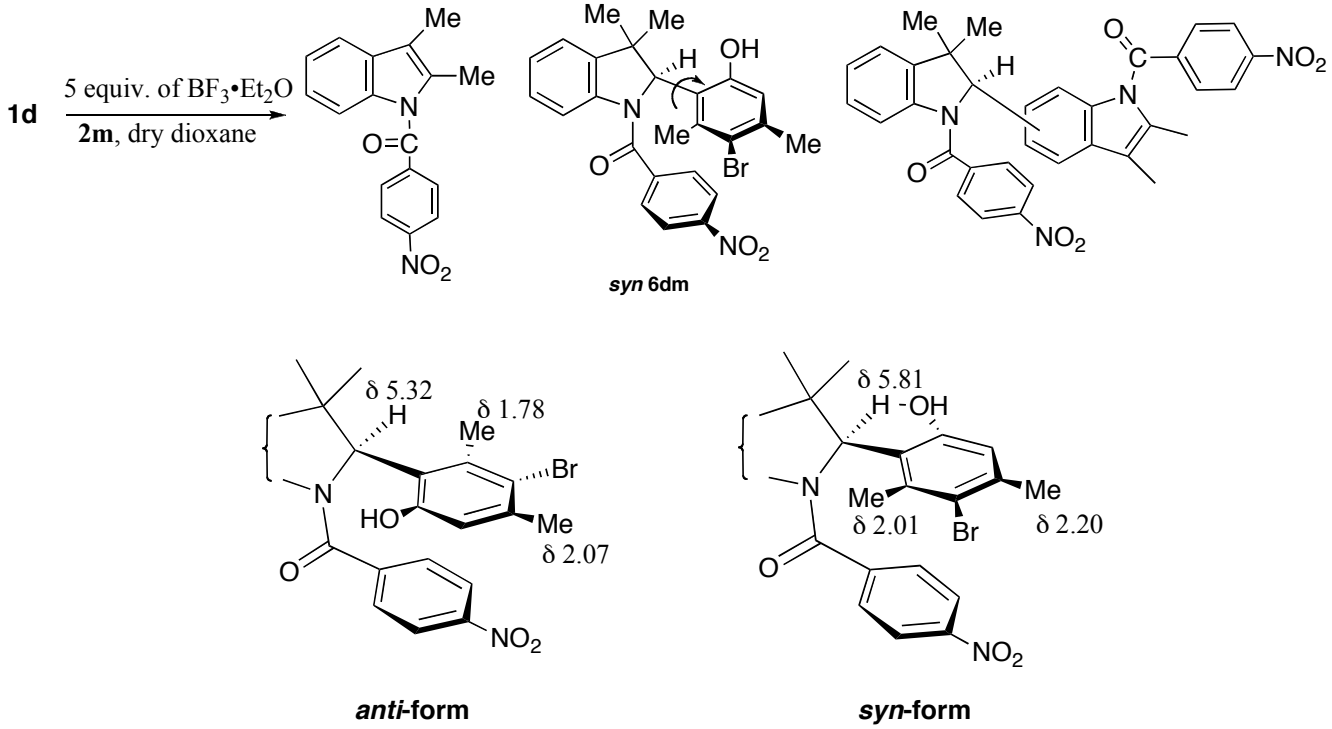


With electron-rich anilines (**2e**, **2g**), the coupling reactions did not occur but gave the oxazine derivatives. These elemental analyses and all the spectral data including the ^{13}C-NMR spectra support the oxazine structure. The anilines presumably stabilize the enol form of the amide, leading to the intermediate (IM) which extrudes formaldehyde to give **8**.



Scheme 6

Finally, mention should be made of isolation of a pair of atropisomers besides the naphthyl derivatives. During the study of the reaction behavior of **1** toward monocyclic aromatic compounds, we isolated a pair of atropisomers (**6dm**) from the reaction of **1d** with 4-bromo-3,5-dimethylphenol (**2m**).



Scheme 7

Heating the reaction product (***syn* 6dm**) in refluxing chloroform caused transformation into an equilibrium mixture of the atropisomers (***anti*/*syn***), which was separated into a pair of atropisomers by chromatography on silica gel. The NMR spectral features are consistent with those observed in the

naphthyl derivatives, in which the ***syn***/***anti*** relationship is defined with respect to the spatial relationship between the C2-H and the OH group of the phenyl ring. This is the first example of a pair of atropisomers isolated from the coupling reaction with monocyclic phenols, indicating that the presence of two substituents at the 2,6-positions of phenyl ring is essential for separation and isolation of the conformers at room temperature.

CONCLUSION

In summary, in the presence of $BF_3 \cdot Et_2O$, (4-chlorophenyl)(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)methanone or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone reacted with 2-amino-naphthalene to give [2-(2-aminonaphthalen-1-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-chlorophenyl)-methanone or 1-[2-(2-aminonaphthalen-1-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl]ethanone, which then cyclized to the 14,14-dimethyl-14,14a-dihydrobenzo[*f*]indolo[1,2-*c*]quinazoline derivatives by dehydration. Of the reactions of several (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)(substituted-phenyl)methanones or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone with various anilines, the reactions with *m*-anisidine gave the 12,12a-dihydroindolo[1,2-*c*]quinazoline derivatives together with the coupling reaction products.

A 12,12a-dihydroindolo[1,2-*c*]quinazoline derivative has been found in a novel marine alkaloid (Hinckdentine A) with potential pharmacological activity.[8] The reaction using the atropisomeric compounds seems to provide a clue for a synthetic method of indoline-condensed quinazoline derivatives.

EXPERIMENTAL

Melting points were uncorrected. The IR spectra were taken with a Hitachi 270-30 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken with JEOL JNM-EX 270 (270 MHz) and JNM-A 500 (500 MHz) spectrometers using TMS as an internal standard; chemical shifts are expressed as δ values and the coupling constants (*J*) are expressed in Hz. UV spectra were recorded on a Shimadzu UV-2500PC spectrophotometer.

Materials

3,3-Dimethylindole and (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)(substituted-phenyl)methanones or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone were prepared by the previously reported methods.[1c] 2-Aminonaphthalene known to be a human carcinogen is not produced for commercial use.

General procedure

$BF_3 \cdot Et_2O$ (5.0 equiv.) was added to a solution of and (2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)-

(substituted-phenyl)methanones or 1-(2-hydroxy-3,3-dimethyl-2,3-dihydroindol-1-yl)ethanone (**1**) and aminoarene (**2**) (2.5 equiv.) in dioxane and the mixture was heated at 60 °C under an Ar atmosphere until the reaction had completed by TLC. After cooling, the reaction mixture was diluted with ether and treated with water. The organic layer was separated, washed with aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The Et_2O was evaporated off. The residue was chromatographed on silica gel. The products separated were crystallized from appropriate solvents.

[2-(4-Aminonaphthalen-1-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-chlorophenyl)methanone (**3ac**)

60% yield; mp 255.0-256.0°C (pale yellow needles from EtOH); *Anal*. Calcd for $C_{27}H_{23}N_2OCl$: C, 75.96; H, 5.43; N, 6.56. Found: C, 75.97; H, 5.41; N, 6.47; νmax (KBr)/cm^{-1} 3456, 3404 (NH_2), 2900-3300 (aromatic C-H), 1620 (C=O), 1588 (C=C); δ_H (500 MHz, DMSO-d_6) 0.76 (3H, s, C3-CH_3), 1.54 (3H, s, C3-CH_3), 5.64 (1H, s, C2-H), 5.70 (2H, br s, NH_2), 6.41 (1H, d, *J*=8.6 Hz), 6.70 (1H, d, *J*=7.9 z), 7.07-7.72 (11H, m), 8.02 (1H, d, *J*=7.3 Hz) ; *m/z* (EI) 426 (M^+).

8-(4-Chlorophenyl)-14,14-dimethyl-14,14a-dihydrobenzo[*f*]indolo[1,2-*c*]quninazoline (**4ab**)

33% yield; mp 198.5-199.5 °C (yellow needles from EtOH); *Anal*. Calcd for $C_{27}H_{21}N_2Cl$: C, 79.30; H, 5.18; N, 6.85. Found: C, 79.48; H, 5.20; N, 6.92; νmax (KBr)/cm^{-1} 2800-3100 (aromatic C-H), 1620 (C=N), 1602 (C=C); δ_H (500 MHz, $CDCl_3$) 1.14 (3H, s, C14-CH_3), 1.61 (3H, s, C14-CH_3), 5.91 (1H, s, C14a-H), 6.27 (1H, d, *J*=7.9 Hz, C10-H), 6.90 (1H, dd, *J*=1.2, 7.9 Hz, C11-H), 7.12 (1H, dt, *J*=1.2, 7.9 Hz, C12-H), 7.17 (1H, dd, *J*=1.2, 7.9 Hz, C13-H), 7.33-7.48 (6H, m), 7.78 (1H, d, *J*=8.5 Hz), 7.82 (1H, d, *J*=7.9 Hz), 7.93 (1H, d, *J*=8.5 Hz); *m/z* (EI) 408 (M^+).

8,14,14-Trimethyl-14,14a-dihydrobenzo[*f*]indolo[1,2-*c*]quinazoline (**4bb**)

34% yield; mp 86.0-88.0 °C (yellow solid); νmax (film)/cm^{-1} 2900-3100 (aromatic C-H), 1694, 1628, 1608 (C=N, C=C), 1572 (C=C); δ_H (270 MHz, $CDCl_3$) 1.02 (3H, s, C14-CH_3), 1.80 (3H, s, C14-CH_3), 2.33 (3H, s, C8-CH_3), 5.72 (1H, s, C14a-H), 7.22-7.27 (4H, m), 7.36-7.44 (3H, m), 7.74-7.88 (3H, m), ; *m/z* (EI) 312 (M^+) [Found : M^+ 312.1606 (EI). $C_{22}H_{20}N_2$ requires M 312.1626].

1-[2-(2,3-dimethylindol-5-yl)-3,3-dimethyl-2,3-dihydroindol-1-yl]ethanone (**5b**)

33% yield; yellow oil; νmax (KBr)/cm^{-1} 2800-3100 (aromatic C-H), 1620 (C=O), 1602 (C=C) ; δ_H (270 MHz, $CDCl_3$) 0.90 (3H, s, C3-CH_3), 1.42 (3H, s, C3-CH_3), 2.02 (3H, s, C_{indole}3-CH_3), 2.18 (3H, s, C_{indole}2-CH_3), 4.95 (1H, s, C2-H), 6.77-6.87 (2H, br), 7.09 (2H, d, *J*=4.6 Hz), 7.27-7.36 (1H, m), 7.64-7.78 (1H, m), 8.54 (1H, d, *J*=7.6 Hz, C7-H) ; *m/z* (EI) 332 (M^+) [Found : M^+ 332.1869 (EI). $C_{22}H_{24}N_2O$ requires M 332.1889].

1-[2-(4-Amino-2-methoxyphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl]ethanone (**6bh**)

52% yield; mp 237.5-238.0 °C (colorless needles from EtOH); *Anal*. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.56; H, 7.16; N, 9.01; νmax (KBr)/cm^{-1} 3460, 3348 (NH_2), 2800-3100

(aromatic C-H), 1648 (C=O), 1618 (C=C); δ_H (300 MHz, $CDCl_3$) 0.96 (3H, s, C3-CH_3), 1.38 (3H, s, C3-CH_3), 1.99 (3H, s, $COCH_3$), 3.72 (2H, br s, NH_2), 3.84 (3H, s, OCH_3), 5.34 (1H, s, C2-H), 6.09 (1H, dd, *J*=2.0, 8.1 Hz, C_{ph}5-H), 6.23 (1H, d, *J*=2.0 Hz, C_{ph}3-H), 6.52 (1H, d, *J*=8.1 Hz, C_{ph}6-H), 7.04-7.08 (2H, m), 7.21-7.26 (1H, m), 8.27 (1H, d, *J*=7.9 Hz, C7-H); *m*/*z* (EI) 310 (M^+).

3-Methoxy-6,12,12-trimethyl-12,12a-dihydroindolo[1,2-*c*]quinazoline (**7bh**)

15% yield; mp 153.5-155.0 °C (colorless needles from EtOH); νmax (KBr)/cm^{-1} 2800-3100 (aromatic C-H), 1582 (C=N), 1558 (C=C); δ_H (300 MHz, $CDCl_3$) 1.04 (3H, s, C12-CH_3), 1.61 (3H, s, C12-CH_3), 2.44 (3H, s, C6-CH_3), 3.81 (3H, s, OCH_3), 5.06 (1H, s, C12a-H), 6.64 (1H, dd, *J*=2.8, 8.4 Hz, C2-H), 6.74 (1H, d, *J*=2.8 Hz, C4-H), 7.04 (1H, d, *J*=8.4 Hz, C1-H), 7.10-7.26 (4H, m, C8, C9, C10, C11-H); *m*/*z* (EI) 292 (M^+). [Found: M^+ 292.1610 (EI). $C_{26}H_{28}N_2O$ requires M 292.1576].

[2-(4-Amino-2-methoxyphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](phenyl)methanone (**6ch**)

31% yield; mp 169.0-169.2 °C (colorless prisms from EtOH); *Anal.* Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49 ; N, 7.52. Found: C, 77.44; H, 6.59; N, 7.55; νmax (KBr)/cm^{-1} 3456, 3348 (NH_2), 2800-3100 (aromatic C-H), 1628 (C=O), 1592 (C=C); δ_H (300 MHz, $CDCl_3$) 0.94 (3H, s, C3-CH_3), 1.37 (3H, s, C3-CH_3), 3.59 (3H, br s, OCH_3), 3.46 (2H, br s, NH_2), 5.27 (1H, br s, C2-H), 6.03 (1H, br s, C_{ph}3-H), 6.09 (1H, dd, *J*=2.0, 8.2 Hz, C_{ph}5-H), 6.59 (1H,d, *J*=8.2 Hz, C_{ph}6-H), 7.09-7.29 (3H, m, C4, C5, C6-H), 8.29 (1H, br s, C7-H); *m*/*z* (EI) 372 (M^+).

3-Methoxy-6-phenyl-12,12-dimethyl-12,12a-dihydroindolo[1,2-*c*]quinazoline (**7ch**)

30% yield (colorless oil); νmax (film)/cm^{-1} 2800-3100 (aromatic C-H), 1584 (C=N), 1554 (C=C); δ_H (300 MHz, $CDCl_3$) 1.17 (3H, s, C12-CH_3), 1.71 (3H, s, C12-CH_3), 3.80 (3H, s, OCH_3), 5.29 (1H, s, C12a-H), 5.76(1H, d, *J*=8.2 Hz, C8-H), 6.70 (1H, dd, *J*=2.2, 7.9 Hz), 6.78 (1H, t, *J*=7.5 Hz), 6.88 (1H, d, *J*=2.6 Hz), 6.96 (1H, t, *J*=7.5 Hz), 7.05-7.45 (7H, m); *m*/*z* (EI) 354 (M^+). [Found: M^+Na 377.1620 (FAB/MeOH+NaI). $C_{24}H_{22}N_2ONa$ requires M 377.1630].

[2-(4-Amino-2-methoxyphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-nitrophenyl)methanone (**6dh**)

46% yield; mp 231.0-232.0 °C (yellow prisms from EtOH); *Anal.* Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.05; H, 5.49; N, 9.98; νmax (KBr)/cm^{-1} 3444, 3348 (NH_2), 2800-3100 (aromatic C-H), 1630 (C=O), 1588 (C=C), 1510, 1348 (NO_2); δ_H (500 MHz, $CDCl_3$) 0.94 (3H, s, C3-CH_3), 1.37 (3H, s, C3-CH_3), 3.66 (3H, br s, OCH_3), 3.81 (2H, br s, NH_2), 5.10 (1H, s, C2-H), 5.98 (1H, s, C_{ph}2-H), 6.11 (1H, dd, *J*=1.8, 7.9 Hz, C_{ph}5-H), 6.58 (1H, d, *J*=7.9 Hz, C_{ph}6-H), 7.13-7.16 (2H, m, C4, C5-H), 7.26 (2H, br s, C_{coph}2, C_{coph}6-H), 7.34 (1H, br s, C6-H), 8.08 (2H, d, *J*=8.5 Hz, C_{coph}3, C_{coph}5-H), 8.33 (1H, br d, C7-H); *m*/*z* (EI) 417 (M^+).

3-Methoxy-6-(4-nitrophenyl)-12,12-dimethyl-12,12a-dihydroindolo[1,2-*c*]quinazoline (**7dh**)

21% yield; mp 168.0-170.0 °C (orange prisms from EtOH); *Anal.* Calcd for $C_{24}H_{21}N_3O_3$ requires: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.26; H, 5.22; N, 10.44; νmax(KBr)/cm^{-1} 2800-3100 (aromatic C-H),

1586 (C=N, C=C), 1602 (C=C), 1552, 1354 (NO_2); δ_H (500 MHz, $CDCl_3$) 1.18 (3H, s, C12-CH_3), 1.71 (3H, s, C12-CH_3), 3.81 (3H, s, OCH_3), 5.30 (1H, s, C12a-H), 5.80 (1H, d, *J*=7.9 Hz, C8-H), 6.75 (1H, dd, *J*=3.0, 8.5 Hz, C2-H), 6.82-6.85 (2H, m, C4, C9-H), 7.03 (1H, dd, *J*=7.3, 6.7 Hz, C10-H), 7.14 (1H, d, *J*=8.5 Hz, C1-H), 7.21 (1H, d, *J*=7.3 Hz, C11-H), 7.67 (2H, br d, *J*=8.5 Hz, $C_{ph}2$, $C_{ph}6$-H), 8.33 (2H, d, *J*=8.5 Hz, $C_{ph}3$, $C_{ph}5$-H) ; *m/z* (EI) 399 (M^+).

[2-(4-Amino-2-methoxyphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](3,5-dinitrophenyl)methanone (6eh)

31% yield; mp 194.0-195.0 °C (orange prisms from EtOH); *Anal.* Calcd for $C_{24}H_{22}N_4O_6$: C, 62.33; H, 4.79; N, 12.11. Found: C, 62.47; H, 4.82; N, 12.05; νmax (KBr)/cm^{-1} 3472, 3388 (NH_2), 2850-3150 (aromatic C-H), 1642 (C=O), 1588 (C=C), 1536, 1344 (NO_2); δ_H (270 MHz, $CDCl_3$) 0.96 (3H, s, C3-CH_3), 1.38 (3H, s, C3-CH_3), 3.42 (3H, br s, OCH_3), 3.71 (2H, br s, NH_2), 5.08 (1H, s, C2-H), 5.94 (1H, d, *J*=1.7 Hz, $C_{ph}2$-H), 6.18 (1H, dd, *J*=2.3, 8.2 Hz, $C_{ph}5$-H), 6.63 (1H, d, *J*=8.2 Hz, $C_{ph}6$-H), 7.15-7.24 (2H, m, C4, C5-H), 7.33-7.88 (1H, t, *J*=6.9 Hz, C6-H), 8.27-8.32 (3H, m, C7, $C_{coph}2$, $C_{coph}6$-H), 8.96 (1H, t, *J*=2.0 Hz, $C_{coph}4$-H) ; *m/z* (EI) 462 (M^+).

3-Methoxy-6-(3,5-dinitrophenyl)-12,12-dimethyl-12,12a-dihydroindolo[1,2-*c*] quinazoline (7eh)

16% yield; mp 90.0-92.0 °C (brown solid); νmax (film)/cm^{-1} 2850-3150 (aromatic C-H), 1594 (C=N, C=C), 1542, 1344 (NO_2); δ_H (270 MHz, $CDCl_3$) 1.19 (3H, s, C12-CH_3), 1.73 (3H, s, C12-CH_3), 3.81 (3H, s, C3-OCH_3), 5.34 (1H, s, C12a-H), 5.83 (1H, d, *J*=7.9 Hz, C8-H), 6.76-7.27 (6H, m), 8.68 (2H, d, *J*=2.0 Hz, $C_{ph}2$, $C_{ph}6$-H), 9.14 (1H, t, *J*=2.0 Hz, $C_{ph}4$-H); *m/z* (EI) 444 (M^+) [Found: M^+ 444.1421 (EI). $C_{24}H_{20}N_4O_5$ requires M 444.1434].

4,4-Dimethyl-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (8d)

27% yield; mp 113.0-114.0 °C (yellow prisms from EtOH); *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.10; H, 5.10; N, 9.86; νmax (KBr)/cm^{-1} 2850-3150 (aromatic C-H), 1592 (C=C), 1514, 1344 (NO_2) ; δ_H (270 MHz, $CDCl_3$) 1.74 (6H, s, C4-$(CH_3)_2$), 7.15-7.36 (4H, m, C5, C6, C7, C8-H), 8.26-8.34 (4H, m, $C_{ph}2$, $C_{ph}3$, $C_{ph}5$, $C_{ph}6$-H); δ_C (125 MHz, $CDCl_3$) 28.6 (C4-$(CH_3)_2$), 79.2 (C4), 149.4 ($C_{ph}4$), 154.5 (C2); *m/z* (EI) 282 (M^+).

[2-(4-Aminophenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-nitrophenyl)methanone (6dd)

42% yield; mp 183.0-184.0 °C (yellow prisms from EtOH); *Anal.* Calcd for $C_{23}H_{21}N_2O_3$ requires: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.11; H, 5.44; N, 10.75; νmax(KBr)/cm^{-1} 3448, 3360 (NH_2), 2800-3200 (aromatic C-H), 1638 (C=O), 1612 (NH_2), 1594 (C=C), 1510, 1344 (NO_2); δ_H (270 MHz, $CDCl_3$) 0.91 (3H, s, C3-CH_3), 1.39 (3H, s, C3-CH_3), 3.61 (2H, br, NH_2), 4.54 (1H, br, C2-H), 6.56 (4H, br d, *J*=5.9 Hz), 7.15 (3H, m), 7.30 (3H, br), 8.13 (2H, d, *J*=8.2 Hz); *m/z* (EI) 387 (M^+).

[2-(4-Dimethylaminophenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-nitrophenyl)methanone (6dj)

45% yield; mp 215.5-216.5 °C (orange plates from EtOH); *Anal.* Calcd for $C_{25}H_{25}N_3O_3$: C, 72.27; H, 6.16;

N, 10.11. Found: C, 72.09; H, 6.05; N, 10.03; νmax (KBr)/cm^{-1} 2800-3100 (aromatic C-H), 1644 (C=O), 1612 (C=C), 1518, 1346 (NO_2) ; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, br s, C3-CH_3), 1.39 (3H, br s, C3-CH_3), 2.90 (6H, s, N(CH_3)$_2$), 4.54 (1H, br s, C2-H), 6.49-7.26 (9H, m), 8.1 (2H, d, *J*=8.1 Hz, C_{ph}3, C_{ph}5-H), 8.31 (1H, br s, C7-H) ; *m*/*z* (EI) 415 (M^+).

[2-(4-Dimethylamino-2-methoxyphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](3,5-dinitrophenyl)-methanone (**6ek**)

84% yield; mp 214.0-215.0 °C (red needles from EtOH); *Anal.* Calcd for $C_{26}H_{26}N_4O_6$: C, 63.66; H, 5.34 ; N, 11.42. Found: C, 63.55; H, 5.37; N, 11.25 ; νmax (KBr)/cm^{-1} 2750-3100 (aromatic C-H), 1648 (C=O), 1612 (C=C), 1538, 1340 (NO_2); δ_H (300 MHz, $CDCl_3$) 0.97 (3H, s, C3-CH_3), 1.40 (3H, s, C3-CH_3), 2.89 (6H, s, N(CH_3)$_2$), 3.44 (3H, s, OCH_3), 5.08 (1H, s, C2-H), 5.84 (1H, s, C_{ph}3-H), 6.19 (1H, dd, *J*=2.2, 8.6 Hz, C_{ph}5-H), 6.69 (1H, d, *J*=8.6 Hz, C_{ph}6-H), 7.06-7.23 (2H, m), 7.33-7.36 (1H, m), 8.21 (2H, s, C_{coph}2, C_{coph}6-H), 8.32 (1H, d, *J*=7.9 Hz, C7-H), 8.91 (1H, d, *J*=1.8 Hz, C_{coph}4-H) ; *m*/*z* (EI) 490 (M^+).

2,3-Dimethoxy-6-(4-nitrophenyl)-12,12-dimethyl-12,12a-dihydroindolo[1,2-*c*]quinazoline (**7dl**)

26% yield; mp 236-238 °C (orange prisms from EtOH); νmax (KBr)/cm^{-1} 2800-3100 (aromatic C-H), 1590 (C=N, C=C), 1560, 1348(NO_2); δ_H (300 MHz, $CDCl_3$) 1.20 (3H, s, C12-CH_3), 1.73 (3H, s, C12-CH_3), 3.88 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.32 (1H, s, C12a-H), 5.83 (1H, d, *J*=8.1 Hz, C8-H), 6.71 (1H, s, C4-H), 6.85 (1H, dd, *J*=7.5, 8.1Hz, C9-H), 6.93 (1H, s, C1-H), 7.04 (1H, dd, *J*=7.3, 7.5Hz, C10-H), 7.22 (1H, d, *J*=7.3 Hz, C11-H), 7.67 (2H, br d, C_{ph}2, C_{ph}6-H), 8.33 (2H, d, *J*=8.5 Hz, C_{ph}3, C_{ph}5-H); *m*/*z* (EI) 429 (M^+) [Found: M^+ 429.1718(EI). $C_{25}N_{23}N_3O_4$ requires M 429.1688].

[2-(3-Bromo-6-hydroxy-2,4-dimethylphenyl)-3,3-dimethyl-2,3-dihydroindol-1-yl](4-nitrophenyl)-methanone (**6dm**)

The ***syn*** atropisomer was isolated in 11% yield. Heating **6dm** in chloroform caused transformation into an equilibrium mixture of the atropisomers (***anti*** /***syn***).

syn mp 246.0-247.0 ℃ (yellow needles from EtOH); ν_{max} (KBr)/cm^{-1} 3148 (OH), 2800-3000 (aromatic C-H), 1614 (NCO), 1584 (C=C), 1524, 1348 (NO_2); δ_H (300 MHz, $CDCl_3$) 1.00 (3H, s, C3-CH_3), 1.50 (3H, s, C3-CH_3), 2.01 (3H, s, C_{ph}6-CH_3), 2.20 (3H, s, C_{ph}4-CH_3), 5.77 (1H, br-s, C_{ph}2-OH), 5.81 (1H, s, C2-H), 6.07 (1H, s, C_{ph}3-H), 7.20-7.31 (5H, m), 7.94 (2H, d, *J*=8.2 Hz, C_{coph}3, C_{coph}5-H), 8.36 (1H, d, *J*=7.9 Hz, C7-H);

anti mp 243.0-244.0 ℃ (yellow powders); ν_{max} (KBr)/cm^{-1} 3256 (OH), 2800-3000 (aromatic C-H), 1624 (NCO), 1588 (C=C), 1520, 1348 (NO_2); δ_H (300 MHz, DMSO-d_6) 1.00 (3H, s, C3-CH_3), 1.49 (3H, s, C3-CH_3), 1.78 (3H, s, C_{ph}6-CH_3), 2.17 (3H, s, C_{ph}4-CH_3), 5.32 (1H, s, C2-H), 6.49 (1H, s, C_{ph}3-H), 7.07-7.12 (1H, m), 7.20-7.25 (2H, m), 7.30 (2H, d, *J*=8.1 Hz, C_{coph}2, C_{coph}6-H), 8.00 (2H, d, *J*=8.1 Hz, C_{coph}3, C_{coph}5-H), 8.24 (1H, d, *J*=7.9 Hz, C7-H), 9.54 (1H, s, OH); *m*/*z* (EI) 494 (M^+). [Found: M^+ 494.0785 (EI). $C_{26}H_{28}N_2O$ requires M 494.0841].

Molecular Orbital (MO) Calculations.

Semi-empirical MO calculations were run through the CS Chem3D Pro interface using MOPAC93 on a Power Macintosh G4 computer. The *ab initio* and density functional theory (DFT) computations[5] were carried out on a HIT parallel computer (Itanium 2, 2 node-4 CPU). The AM1-optimized structures were used as starting geometries for the *ab initio* and DFT calculations. The B3LYP/6-31G* calculated data are available upon request through E-mail.

Single Crystal X-Ray Analysis of 4ab and 6dj

A yellow prism crystal having approximate dimensions of 0.30 x 0.30 x 1.00 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 23 ± 1 °C to a maximum 2θ value of 55.0°. The structures were solved by direct method (SIR-92)[9], and hydrogen atoms were placed at the calculation. A full-matrix least-squares technique was using with anisotropic thermal parameters for non-hydrogen atoms and riding model for hydrogen atoms. All calculations were performed using the Crystal Structure[10,11] crystallographic software package.

4ab; $C_{54}H_{42}Cl_2N_4$ (two molecules), F.W. = 817.86, orthorhombic. The systematic absences of: h00: h ± 2n, 0k0: k ± 2n, 00l: l ± 2n, uniquely determine the space group to be: $P2_12_12_1$ (#19). *a*=6.1411(5), *b*=22.447(2), *c*=30.654(3) Å, *V*=4225.7(7) Å^3, *Dc*=1.29 gcm^{-3}, *Z*=4, *R*=0.068 for 3744 observed reflections ($I > 3.00\sigma(I)$), *Rw*=0.122. The crystallographic data are deposited to CCDC (reference number, 626516).

Similarly, the crystal structure of **6dj** was determined. Crystal Data of **6dj**; $C_{25}H_{25}N_3O_6$, M=415.49, monoclinic, space group $P2_1/n$, *a*=7.3530 (4), *b*=13.013 (1), *c*=23.436 (1) Å, β=94.841 (1) °, *V*=2234.4 (2) Å^3, *Dc*=1.24 gcm^{-3}, *Z*=4, *R*=0.088 for 3521 observed reflections ($I > 0.5\sigma(I)$), *Rw*=0.116, CCDC reference number, 626517.

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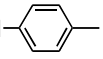
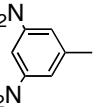
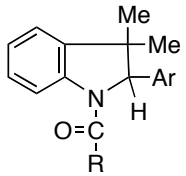
4. a) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902. b) AM1 calculations were run through the CS Chem3D Pro interface using MOPAC97 on a Power Macintosh G4 computer. c) The AM1 method is suitable for the structure optimization of atropisomers involving amide groups.[1d] The PM3 method could not reproduce the sp^2 nature of the amide group of the 1-aroylindoline moiety.
5. a) The colors of the coupling reaction products are summarized as follows.

R \ Ar	H_2N-	H_2N-(OMe)	Me_2N-	Me_2N-(OMe)
Me-		**6bh** Colorless		
		**6ch** Colorless		
O_2N- 	**6dd** yellow	**6dh** yellow	**6dj** orange	
O_2N-  $-NO_2$		**6eh** orange	**6ej** red	**6ek** red



The UV–vis spectra of **6** showed long absorption tailings up to 500 nm and the difference spectra gave broad peaks around 420-nm. The molar absorptivities at 420 nm are 205.4 for **6dj**, 413.2 for **6eh** and 376.6 for **6ej**.

b) The closest intra- and intermolecular distances between the 4-dimethylaminophenyl and 4-nitrophenyl rings in the crystal structure of **6dj** are 3.323 and 3.473Å, respectively.

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