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ROLE OF 2-NAPHTHYL ETHER INTERMEDIATE IN FORMATION OF ISOLABLE ATROPISOMERS DERIVED FROM THE COUPLING REACTION OF (2-HYDROXY-3,3-DIMETHYLINDOLIN-1-YL)-(SUBSTITUTED PHENYL)METHANONES WITH 2-NAPHTHOL

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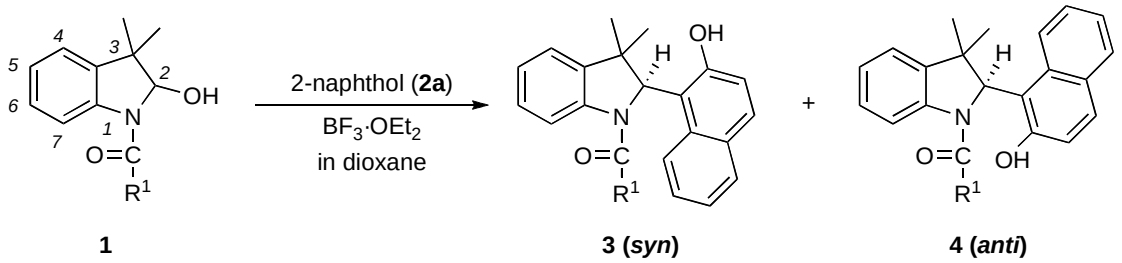
Abstract – The formation pathway of the atropisomers derived from the reaction of (2-hydroxy-3,3-dimethylindolin-1-yl)(4-substituted phenyl)methanones with 2-naphthol in the presence of BF_3•Et_2O was discussed on the basis of the isolation of the 2-naphthyl ether intermediate whose structure was determined by single crystal X-ray analysis. The results indicate that the coupling reaction proceeds through stepwise mechanism, *i.e.*, the ether intermediate formation followed by Fries-type rearrangement.

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-dimethylindolin-1-yl)(substituted phenyl)-methanones (so-called, 1-acyl-2-hydroxy-3,3-dimethylindolin, **1**) with various electron-rich aromatic compounds (*e.g.*, 2-naphthol, **2a**) in the presence of boron trifluoride diethyl ether (BF_3•Et_2O).[1c] The reaction proceeds under mild reaction conditions and provides an important method for synthesis of isolable diastereomeric atropisomers (**3** and **4**) arising from restricted rotation around a Csp^3-Csp^2 bond (Scheme 1).[2] We have isolated 16 pairs of atropisomers and clarified important structural features and characterized weak interactions intervened in the restricted rotation.

During the course of the study of the coupling reaction of (2-hydroxy-3,3-dimethylindolin-1-yl)(4-nitrophenyl)methanone (**1a**) with 4-methylphenol (**2b**), we isolated the corresponding ether

derivative (**6ab**) besides the 2-aryl derivative (**7ab**) and the elimination product (**5a**) *via* the Wagner-Meerwein type rearrangement.

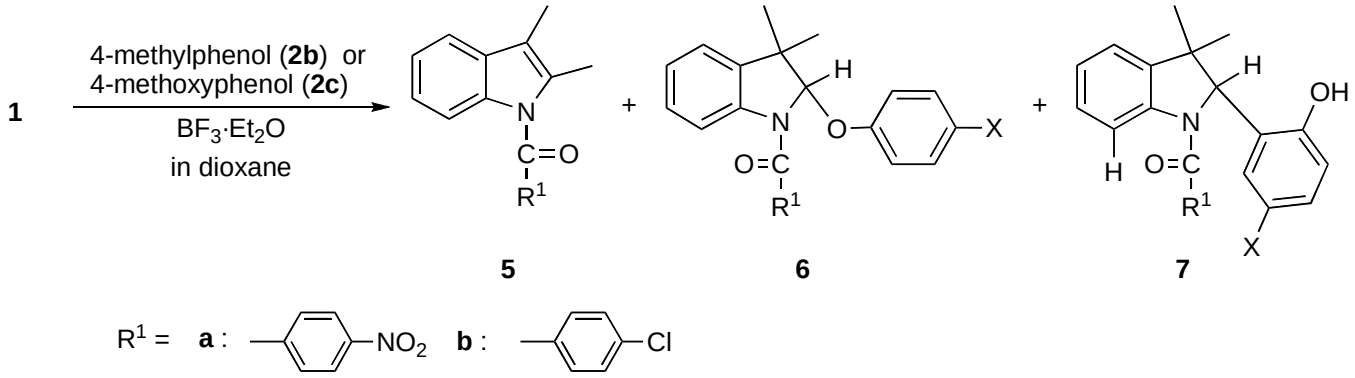


Scheme 1

This paper describes a possible formation pathway of the atropisomers in connection with the isolation of the intermediary phenyl ethers.

RESULTS AND DISCUSSION

The reaction of **1a** (4-nitrophenyl derivative) with 4-methylphenol (**2b**) in the presence of BF_3•Et_2O at room temperature for 2 hr gave **6ab** and **7ab** in 38 and 24% yields, respectively.



Substrate	Phenol	Solvent	Temp (°C)	Time (h)	Yield (%) 6	7	5
1a	**2b**	dioxane	rt	0.5	33 (**6ab**)	19 (**7ab**)	1 (**5a**)
1a	**2b**	dioxane	rt	2	38 (**6ab**)	24 (**7ab**)	3 (**5a**)
1a	**2b**	dioxane	rt	6	4 (**6ab**)	66 (**7ab**)	4 (**5a**)
1a	**2b**	Et_2O	rt	3	44 (**6ab**)	-	-
1a	**2c**	Et_2O	rt	3	55 (**6ac**)	-	-
1b	**2b**	dioxane	rt	72	-	19 (**7bb**)	13 (**5b**)
1b	**2b**	Et_2O	0	2	71 (**6bb**)	-	-
1b	**2c**	Et_2O	rt	5	-	59 (**7bc**)	-
1b	**2c**	Et_2O	0	1.5	22 (**6bc**)	-	-

Scheme 2

The yields of the reaction products under various reaction conditions are summarized in Scheme 2. As can be seen in Scheme 2, the formation of the phenyl ether derivative (**6**) is preferred for short reaction times in ethereal solvents at room temperature and when the reaction was performed under milder reaction conditions, the product ratio (**7**/**6**) decreased with an increase of the 2-phenyl ether derivative (**6**).

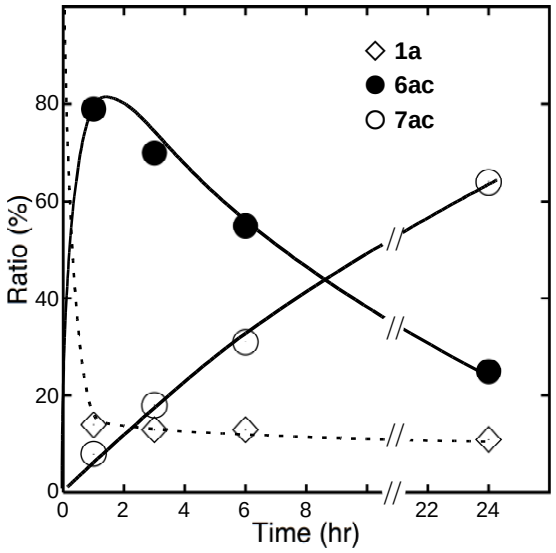
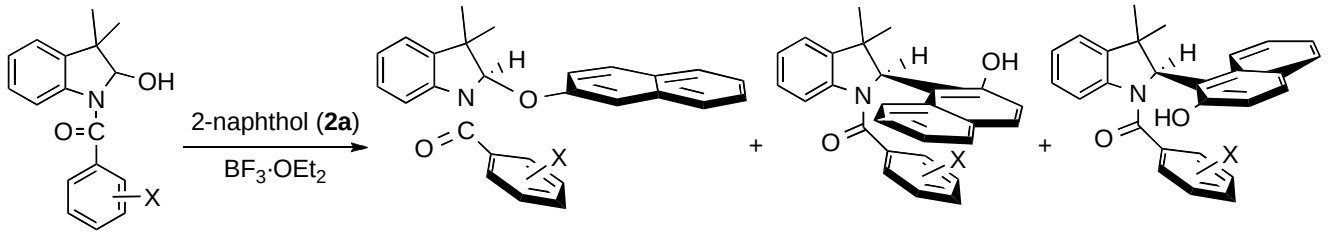


Figure 1. Time Cource of Reaction of **1a** with **2c** in Et_2O in the Presence of BF_3•Et_2O

In order to confirm the isomerization of **6** to **7**, the time-course study in Et_2O was performed. As depicted in Figure 1, at the early stage of the reaction, the 2-phenyl ether (**6ac**) formed rapidly and immediately reached a maximum point, and decreased with increase of the 2-aryl derivative (**7ac**), indicating that the phenol ether derivative is an intermediary product, at least, in the reaction condition used. This assumption is supported by the fact that **6ab** was treated with BF_3·Et_2O in dioxane at room temperature to give the corresponding 2-aryl derivative **7ab** (20%) besides **5a** (6%) and **1a** (6%).



1 **8** **3** (***syn***) **4** (***anti***)

X = **a**: 4-NO_2 **b**: 4-Cl **c**: 4-H **d**: 3-CH_3 **e**: 2-NO_2

Substrate	Solvent	Temp (°C)	Time (h)	Yield (%) **8**	**3** (***syn***)	**4** (***anti***)
1a	dioxane	rt	24	-	27 (**3aa**)	53 (**4aa**)
1a	Et_2O	0	3	59 (**8aa**)	-	-
1b	dioxane	rt	24	-	29 (**3ba**)	45 (**4ba**)
1b	Et_2O	0	3	15 (**8ba**)	16 (**3ba**)	28 (**4ba**)
1c	dioxane	rt	24	-	18 (**3ca**)	58 (**4ca**)
1c	Et_2O	0	3	8 (**8ca**)	11 (**3ca**)	28 (**4ca**)
1d	dioxane	rt	24	-	38 (**3da**)	43 (**4da**)
1d	Et_2O	0	3	13 (**8da**)	12 (**3da**)	19 (**4da**)
1e	Et_2O	0	3	65 (**8ea**)	-	-

Scheme 3

In the case of 2-naphthol (**2a**), we have not yet isolated [3,3-dimethyl-2-(naphthalen-2-yloxy)-indolin-1-yl](4-nitrophenyl)methanone (**8aa**). Therefore the reaction was reexamined under reaction conditions similar to those used for monocyclic phenols described above.

When the reaction was carried out in an ice bath using diethyl ether as solvent, we found that the 2-naphthyl ether compound (**8aa**) was produced in 59% yield. Similarly, 2-nitrobenzoyl derivative (**1e**) gave only the 2-naphthyl ether (**8ea**) in good yield. On the other hand, the 4-chlorobenzoyl (**1b**), benzoyl (**1c**) and 3-methylbenzoyl (**1d**) derivatives of **1** gave mixtures of the ether derivative and a pair of atropisomers (Scheme 3).

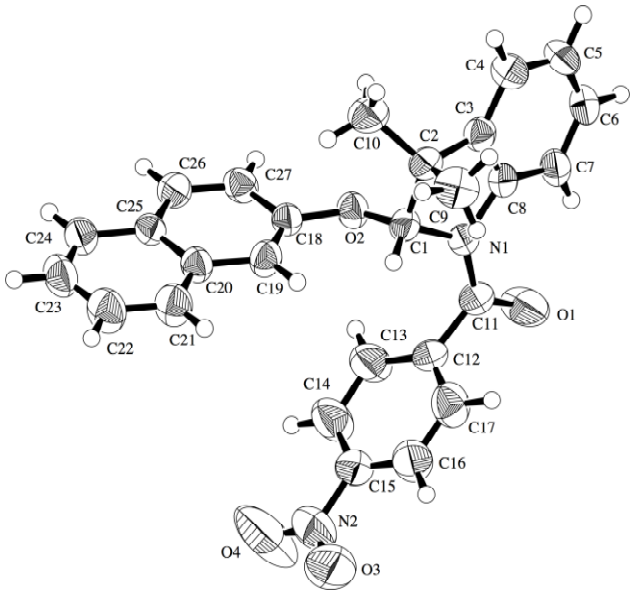
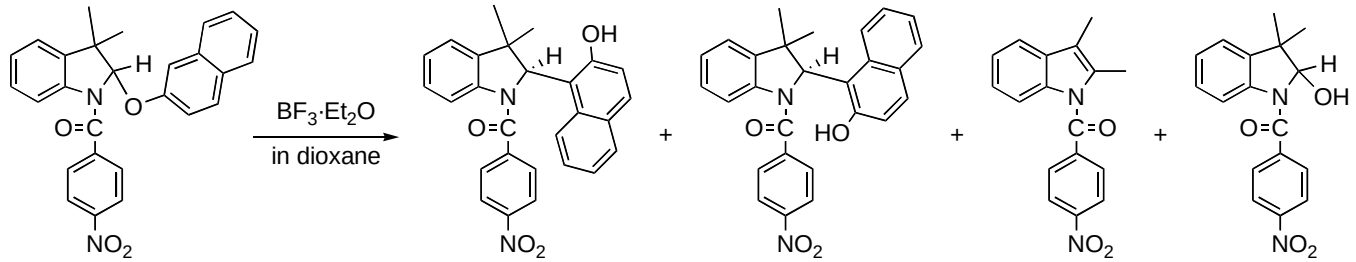


Figure 2. ORTEP Drawing of **8aa**

The structure of **8aa** was confirmed by single crystal X-ray analysis. The computer-generated molecular structure[3] is depicted in Figure 2.

The ether **8aa** was treated with BF_3•Et_2O to give a mixture of *syn* and *anti* atropisomers (**3aa**, **4aa**) besides **5a** and **1a** (Scheme 4). The observed *syn*:*anti* product ratio (*ca*. 1:2) is identical with that observed in the BF_3•Et_2O-catalyzed coupling reaction of the 2-hydroxyindoline derivative (**1a**) with 2-naphthol (**2a**) at rt.

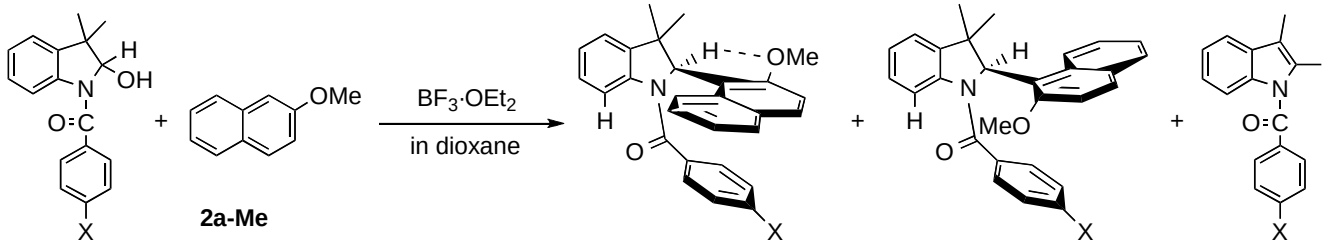
However, the *syn/anti* product ratio is quite different from that observed in its equilibrium reaction products. Heating **4aa** (*anti*) in 1,4-dioxane at 60 °C for 72 h caused transformation into an equilibrium mixture of the atropisomers [**3aa** (*syn*) / **4aa** (*anti*) = 1.2]. This indicates that the $BF_3 \cdot Et_2O$-catalyzed rearrangement reaction products from the 2-naphthyl ether are kinetically controlled ones.



Scheme 4

Next, we explored the possibility of direct Friedel-Craft type reaction using 2-methoxynaphthol (**2a-Me**) under the reaction conditions used in the previous study (Scheme 5). Inspection of the ^{1}H-NMR spectrum of the coupling products (**9a** and **10a**) showed a regularly observed characteristic spectral feature attributable to a pair of the atropisomers,[1b] in which a downfield shift of >C2-H proton signal was recognized in the *syn* isomer due to C-H•••O< type weak interaction[4] [δ 6.13 (*syn*), δ 5.73 (*anti*)].

The reaction with **2a-Me** was found to proceed significantly slower than the reaction with **2a**, showing an increase of the elimination product (**5**) *via* the Wagner-Meerwein type rearrangement. This fact indicates that the product *via* direct Friedel-Craft reaction is present in only small amounts at least under the reaction condition used.



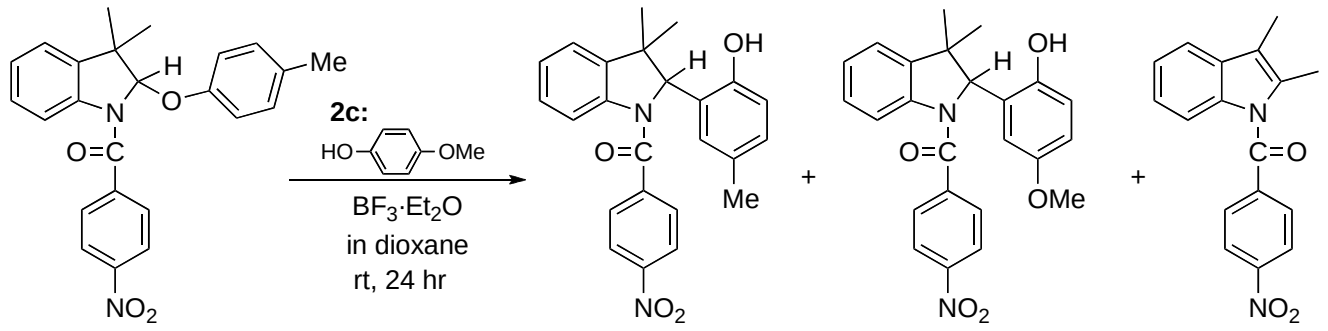
1 **2a-Me** **9** (*syn*) **10** (*anti*) **5**

X = **a** : NO_2 , **b** : Cl , **c** : H

Substrate	Temp (°C)	Time (h)	Yield (%) **9** (***syn***)	**10** (***anti***)	**5**
1a	**rt**	48	12 (**9a**)	25 (**10a**)	32 (**5a**)
1b	**rt**	70	15 (**9b**)	65 (**10b**)	19 (**5b**)
1c	**rt**	48	9 (**9c**)	38 (**10c**)	21 (**5c**)

Scheme 5

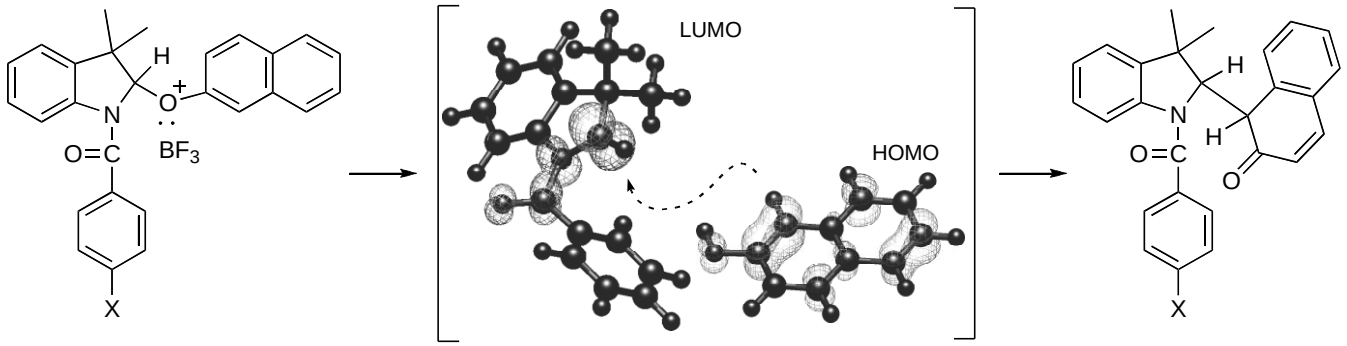
In the Lewis-acid catalyzed rearrangement of phenolic ethers, evidence has been found for inter- and intramolecular processes.[5] The intermolecular nature of the reaction was confirmed by the exchange reaction of **6ab** with external-additive 4-methoxyphenol (**2c**). The reaction gave the non-exchanged product (**7ab**) and the exchange product (**7ac**) in 26% and 24% yields, respectively (Scheme 6).



6ab **7ab** 26% **7ac** 24% **5a** 5%

Scheme 6

The result of the exchange reaction suggests that the rearrangement reaction is considered to proceed partly through an intramolecular pathway because the non-exchanged reaction product (formally speaking) persists in the reaction product although there exists a large excess of phenols during the whole reaction period. The non-exchanged reaction product was presumably derived from the internal return of the external ion-pair intermediate (a loosely-dissociated ion-pair intermediate) rather than free ions in view of the low dielectric constant of the solvent (1,4-dioxane, ε=2.2) comparable to that of benzene. The recombination behavior of the ion pair may be explained by the primary FMO (frontier molecular orbital) interaction[6] between the largest LUMO coefficient (C2) of indoline cation and the largest HOMO coefficient (C1) of the naphthol (Scheme 7).



Scheme 7

In conclusion, the formation reaction of the diastereomeric atropisomers in the BF_3•Et_2O-catalyzed coupling reaction of **1** with **2** proceeds through the 2-naphthyl ether intermediate followed by Fries-type rearrangement.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured on a HITACHI 270-30 IR spectrophotometer. NMR spectra were taken with JNM-EX 270, JNM-AL 300, JNM-GX 400 and JNM-A 500 NMR spectrometers in $CDCl_3$ or DMSO-d_6 solution, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ (ppm) and coupling constants (*J*) are described as Hz. EI MS and high resolution MS (HR-MS) spectra were measured on a JEOL GC-Mate spectrometer.

Materials (2-Hydroxy-3,3-dimethylindolin-1-yl)(substituted phenyl)methanones (**1a-e**) were prepared by addition of substituted benzoyl chloride to 3,3-dimethyl-3*H*-indole followed by treatment of the corresponding 2-chloro derivatives with water.[1c] Phenols were commercially available compounds.

Reaction of 1 with phenolic compounds 2 (General procedure) BF_3·Et_2O (10.0 mmol) was added to

a solution of (2-hydroxy-3,3-dimethylindolin-1-yl)(substituted phenyl)methanones (**1**) (2.0 mmol) and phenols (**2**) (4.0 mmol) in dry dioxane (10 mL) and the mixture was heated at given temperature under an Ar atmosphere until the reaction had completed by TLC. After cooling, the reaction mixture was diluted with Et_2O (200 mL) 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 eluting with benzene/EtOAc (100:1). The products separated were crystallized from appropriate solvent.

Reaction of 1a with monocyclic phenols (2b-c) According to the general procedure, the reaction of **1a** (2.0 mmol) with monocyclic phenols in dry dioxane (at rt) or ether (at 0 °C or rt) was carried out in the presence of $BF_3 \cdot Et_2O$ for given hour to give **6**, **7** and **5a**.

[3,3-Dimethyl-2-(4-tolyloxy)indolin-1-yl](4-nitrophenyl)methanone (6ab) Yellow plates from EtOH; mp 176-179 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.38 (3H, s, C3-Me), 1.43 (3H, s, C3-Me), 2.26 (3H, s, C_{Ar}4-Me), 5.66 (1H, s, C2-H), 6.52 (2H, br s, C_{Ar}2, C_{Ar}6-H), 6.92 (2H, d, *J*= 8.3 Hz, C_{Ar}3, C_{Ar}5-H), 7.19-7.29 (3H, m, C4, C5, C6-H), 7.41 (2H, d, *J*= 8.6 Hz, C_{COAr}2, C_{COAr}6-H), 8.02 (3H, br d, *J*= 8.6 Hz, C_{COAr}3, C_{COAr}5-H, C7-H); MS m/z: 402 (M^+); *Anal*. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.14; H, 5.49; N, 6.73; IR (KBr) cm^{-1}: 1666 (NC=O), 1601 (C=C), 1478, 1344 (NO_2).

[2-(2-Hydroxy-5-methylphenyl)-3,3-dimethyl-indolin-1-yl](4-nitrophenyl)methanone (7ab) Pale yellow powder from EtOH; mp 273-279 °C; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ: 0.92 (3H, s, C3-Me), 1.41 (3H, s, C3-Me), 2.05 (3H, s, C_{Ar}5-Me), 5.26 (1H, s, C2-H), 6.43 (1H, s, C_{Ar}6-H), 6.48 (1H, br d, *J*= 7.9 Hz, C_{Ar}4-H), 6.81 (1H, d, *J*= 7.9 Hz, C_{Ar}3-H), 7.18-7.37 (5H, m, aromatic C-H), 8.11 (2H, br s, C_{COAr}3, C_{COAr}5-H), 8.26 (1H, br s, C7-H), 9.00 (1H, br s, C_{Ar}2-OH); MS m/z: 402 (M^+); *Anal*. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.81; H, 5.47; N, 7.16; IR (KBr) cm^{-1}: 3420 (OH), 1630 (NC=O), 1601 (C=C), 1524, 1348 (NO_2).

[2-(4-Methoxyphenoxy)-3,3-dimethylindolin-1-yl](4-nitrophenyl)methanone (6ac) Yellow plates from EtOH; mp 129-131 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (3H, s, C3-Me), 1.47 (3H, s, C3-Me), 3.75 (3H, s, C_{Ar}4-OMe), 5.62 (1H, br s, C2-H), 6.58 (2H, br s, C_{Ar}2, C_{Ar}6-H), 6.66 (2H, d, *J*= 8.9 Hz, C_{Ar}3, C_{Ar}5-H), 7.20-7.26 (3H, m, C4, C5, C6-H), 7.34 (2H, d, *J*= 8.3 Hz, C_{COAr}2, C_{COAr}6-H), 8.05 (3H, br d, *J*= 8.3 Hz, C_{Ar}3, C_{Ar}5-H, C7-H); MS m/z: 418 (M^+); *Anal*. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.82; H, 5.27; N, 6.57; IR (KBr) cm^{-1}: 1648 (NC=O), 1596 (C=C), 1518, 1344 (NO_2).

[2-(2-Hydroxy-5-methoxyphenyl)-3,3-dimethylindolin-1-yl](4-nitrophenyl)methanone (7ac)

Yellow needles from EtOH; mp 253-254 °C; ^{1}H-NMR (300MHz, DMSO-*d*$_6$) δ: 0.93 (3H, s, C3-Me), 1.41 (3H, s, C3-Me), 3.51 (3H, s, C_{Ar}5-OMe), 5.23 (1H, s, C2-H), 6.14 (1H, d, *J*= 2.9 Hz, C_{Ar}6-H), 6.55 (1H, br d, *J*= 8.6 Hz, C_{Ar}3-H), 6.64 (1H, dd, *J*= 2.9, 8.6 Hz, C_{Ar}4-H), 7.18-7.29 (3H, m, C4, C5, C6-H), 7.38 (2H, br s, C_{COAr}2, C_{COAr}6-H), 8.13 (2H, br s, C_{COAr}3, C_{COAr}5-H), 8.24 (1H, br s, C7-H), 8.81 (1H, br s,

C_{Ar}2-OH); MS m/z: 418 (M^+); *Anal*. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.72; H, 5.24; N, 6.84; IR (KBr) cm^{-1}: 3448 (OH), 1634 (NC=O), 1592 (C=C), 1508, 1346 (NO_2).

(4-Chlorophenyl)[3,3-dimethyl-2-(4-tolyloxy)indolin-1-yl]methanone (6bb) Colorless prisms from EtOH; mp 154-156 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.35 (3H, s, C3-Me), 1.42 (3H, s, C3-Me), 2.28 (3H, s, C_{Ar}4-Me), 5.77 (1H, s, C2-H), 6.57 (2H, d, *J*= 7.7 Hz, C_{Ar}2, C_{Ar}6-H), 6.96 (2H, d, *J*= 8.4 Hz, C_{COAr}3, C_{COAr}5-H), 7.12-7.25 (3H, m, C4, C5, C6-H), 7.17 (2H, d, *J*= 8.4 Hz, C_{COAr}3, C_{COAr}5-H), 7.24 (2H, d, *J*= 7.7 Hz, C_{Ar}2, C_{Ar}6-H), 7.80 (1H, br s, C7-H); MS m/z: 391 (M^+); *Anal*. Calcd for $C_{24}H_{22}ClNO_2$: C, 73.56; H, 5.66; N, 3.57. Found: C, 73.85; H, 5.70; N, 3.47; IR (KBr) cm^{-1}: 1666 (NC=O), 1594 (C=C).

(4-Chlorophenyl)[2-(2-hydroxy-5-methylphenyl)-3,3-dimethylindolin-1-yl]methanone (7bb) Colorless powder from EtOH; mp 228-230 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.93 (3H, s, C3-Me), 1.40 (3H, s, C3-Me), 2.03 (3H, s, C_{Ar}5-Me), 5.35 (1H, s, C2-H), 6.42 (1H, s, C_{Ar}6-H), 6.59 (1H, br s, C_{Ar}4-H), 6.81 (1H, d, *J*= 7.9 Hz, C_{Ar}3-H), 7.16-7.36 (7H, m, aromatic C-H), 8.22 (1H, br s, C7-H), 9.18 (1H, br s, C_{Ar}2-OH); MS m/z: 391 (M^+); *Anal*. Calcd for $C_{24}H_{22}ClNO_2$: C, 73.56; H, 5.66; N, 3.57. Found: C, 73.41; H, 5.45; N, 3.57; IR (KBr) cm^{-1}: 3500-3200 (OH), 1622 (NC=O), 1588 (C=C).

(4-Chlorophenyl)[2-(4-methoxyphenoxy)-3,3-dimethylindolin-1-yl]methanone (6bc) Colorless prisms from EtOH; mp 154-156 °C; ^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.37 (3H, s, C3-Me), 1.46 (3H, s, C3-Me), 3.77 (3H, s, C_{Ar}4-OMe), 5.73 (1H, s, C2-H), 6.62 (2H, br s C_{Ar}2, C_{Ar}6-H), 6.70 (2H, br s C_{Ar}3, C_{Ar}5-H), 7.07-7.52 (7H, m, aromatic C-H), 7.83 (1H, br s, C7-H). MS m/z: 407 (M^+); *Anal*. Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43. Found: C, 70.80; H, 5.41; N, 3.41; IR (KBr) cm^{-1}: 1658 (NC=O), 1592 (C=C).

(4-Chlorophenyl)[2-(2-hydroxy-5-methoxyphenyl)-3,3-dimethylindolin-1-yl]-methanone (7bc) Colorless powder from EtOH; mp 248-249°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.93 (3H, s, C3-Me), 1.38 (3H, s, C3-Me), 3.48 (3H, s, C_{Ar}5-OMe), 5.32 (1H, s, C2-H), 6.13 (1H, s, C_{Ar}6-H), 6.61 (2H, s, C_{Ar}3, C_{Ar}4-H), 7.10-7.39 (7H, m, aromatic C-H), 8.18 (1H, br s, C7-H), 9.00 (1H, br s, C_{Ar}2-OH); MS m/z: 407 (M^+); *Anal*. Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43. Found: C, 70.35; H, 5.44; N, 3.43; IR (KBr) cm^{-1}: 3500-3300 (OH), 1628 (NC=O), 1590 (C=C).

Catalytic Rearrangement of 6ab to 7ab A solution of **6ab** (1.0 mmol) in dry dioxane (5 mL) containing $BF_3 \cdot Et_2O$ (5.0 mmol) was stirred at room temperature for 24 hr. The same work-up as described in the general procedure gave **7ab**, **5a** and **1a**.

Phenol-exchange reaction of 6ab A solution of **6ab** (0.5 mmol) and **2c** (0.5 mmol) in dry dioxane (5 mL) containing $BF_3 \cdot Et_2O$ (2.5 mmol) was stirred at rt for 24 h. The same work-up as described in the general procedure gave **7ab**, **7ac** and **5a**.

Time Course of reaction of 1a with 2c $BF_3 \cdot Et_2O$ (10.0 mmol) was added to a solution of **1a** (2.0 mmol) and *p*-methoxyphenols (**2c**) (4.0 mmol) in dry Et_2O (10 mL) and the mixture was stirred at 0 °C under an Ar atmosphere. At appropriate intervals of time, a small amount of the reaction mixture was

withdrawn by a syringe, quenched with water, and extracted with Et_2O. After evaporation of the solvent under reduced pressure, the residue was analyzed by ^{1}H-NMR. The relative ratio of the reaction product (**6ac**, **7ac**) and **1a** were evaluated by the spectral integration of the methyl group.

Reaction of 1a-e with 2a (Formation of the naphthyl ether 8aa-ea) A solution of **1a** (1.0 mmol) and **2a** (1.0 mmol) in dry dioxane (5 mL) containing $BF_3 \cdot Et_2O$ (5.0 mmol) was stirred at 0 °C. The same work-up as described in the general procedure gave **8aa**. Similarly, the reactions of **1b-e** with **2a** gave the corresponding products, respectively.

[3,3-Dimethyl-2-(naphthalen-2-yloxy)indolin-1-yl](4-nitrophenyl)methanone (8aa) Yellow plates from EtOH; mp 154-156 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.45 (3H, s, C3-Me), 1.48 (3H, s, C3-Me), 5.92 (1H, br s, C2-H), 6.91-7.85 (15H, m, aromatic C-H); MS m/z: 438 (M^+), 295 (M^+-143); *Anal*. Calcd. for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 74.04; H, 5.00; N, 6.41; IR (KBr) cm^{-1}: 1660 (NC=O), 1480, 1346 (NO_2), 998 (-O-).

(4-Chlorophenyl)[3,3-dimethyl-2-(naphthalen-2-yloxy)-indolin-1-yl]methanone (8ba) Colorless prisms from EtOH, mp 159-161 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41 (3H. s, C3-Me), 1.46 (3H, s, C3-Me), 6.01 (1H, s, C2-H), 6.90-7.77 (15H, m, aromatic C-H); MS m/z : 427 (M^+), 284 (M^+-143); *Ana1*. Calcd. for $C_{27}H_{22}C1NO_2$: C, 75.78; H, 5.18; N, 3.27. Found: C, 75.72; H, 4.96; N, 3.17; IR (KBr) cm^{-1}: 3160-2850 (aromatic C-H), 1662 (NC=O), 1594 (C=C), 1002 (-O-).

[3,3-Dimethyl-2-(naphthalen-2-yloxy)indolin-1-yl]-(phenyl)methanone (8ca) Colorless prisms from EtOH, mp 107-108 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41 (3H, s, C3-Me), 1.44 (3H, s, C3-Me), 6.04 (1H, s, C2-H), 6.84-7.74 (15H, m, aromatic C-H), 7.75 (1H, brs, C7-H); MS m/z: 393 (M^+), 250 (M^+-143); *Ana1*. Calcd. for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.63; H, 5.91; N, 3.61; IR (KBr) cm^{-1}: 3050-2800 (aromatic C-H), 1656 (NC=O), 1596 (C=C), 992 (-O-).

[3,3-Dimethyl-2-(naphthalen-2-yloxy)indolin-1-yl](3-tolyl)methanone (8da) Colorless powder from EtOH, mp 109-111 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41 (3H, s, C3-Me), 1.44 (3H, s, C3-Me), 1.86 (3H, s, C_{Ar}3-Me), 6.00 (1H, s, C2-H), 6.84-7.75 (14H, m, aromatic C-H), 7.93 (1H, brs, C7-H); MS m/z: 407 (M^+), 264 (M^+-143); *Ana1*. Calcd. for $C_{28}H_{25}NO_2$: C, 82.53; H, 6.18; N, 3.44. Found: C, 82.28; H, 6.10; N, 3.26; IR (KBr) cm^{-1}: 3052-2868 (aromatic C-H), 1660 (NC=O), 1596 (C=C), 990 (-O-).

[3,3-Dimethyl-2-(naphthalen-2-yloxy)indolin-1-yl](2-nitrophenyl)methanone (8ea) Yellow plates from EtOH, mp 158-160 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.36 (3H, s, C3-Me), 1.44 (3H, s, C3-Me), 5.64 (1H, brs, C2-H), 6.45-8.30 (14H, m, aromatic C-H), 8.00 (1H, brs, C7-H); MS m/z: 438 (M^+), 295 (M^+-143). *Ana1*. Calcd. for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.69; H, 4.96; N, 6.49. IR (KBr) cm^{-1}: 3100-2950 (aromatic C-H), 1664 (NC=O), 1598 (C=C), 1484, 1350 (NO_2), 1006 (-O-).

Catalytic Rearrangement of 8aa to 3aa and 4aa A solution of **8aa** (0.7 mmol) in dry dioxane (5 mL)

containing $BF_3 \cdot Et_2O$ (5.0 mmol) was stirred at rt or 60 °C for 24 h. The same work-up as described in the general procedure gave **3aa**, **4aa**, **5a** and **1a**.

Reaction of 1a-c with 2-methoxynaphthalene 2a-Me A solution of **1a-c** (1.0 mmol) and **2a-Me** (1.0 mmol) in dry dioxane (5 mL) containing $BF_3 \cdot Et_2O$ (5.0 mmol) was stirred at rt. The same work-up as described in the general procedure gave **5a-c**, **9a-c** and **10a-c**.

[2-(2-Methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](4-nitrophenyl)methanone (9a) (*syn)* Pale yellow prisms from EtOH; mp 210-211 °C; ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.98 (3H, s, C3-Me), 1.60 (3H, s, C3-Me), 3.60 (3H, s, C_{naph}2-OMe), 6.13 (1H, s, C2-H), 6.72-7.79 (13H, m, aromatic C-H), 8.51 (1H, d, *J*= 7.9 Hz, C7-H); MS m/z: 452 (M^+). *Anal*. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.39; H, 5.11; N, 6.25; IR (KBr) cm^{-1}: 1644 (NC=O), 1594 (C=C), 1514, 1346 (NO_2).

[2-(2-Methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](4-nitrophenyl)methanone (10a) (*anti)* Yellow prisms from EtOH; mp 175-176 °C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.01 (3H, s, C3-Me), 1.63 (3H, s, C3-Me), 3.48 (3H, s, C_{naph}2-OMe), 5.73 (1H, s, C2-H), 6.89 (1H, d, *J*= 8.3 Hz, C_{naph}3-H), 7.13-7.36 (7H, m, aromatic C-H), 7.23 (1H, d, *J*= 8.3 Hz, C_{naph}4-H), 7.55 (2H, d, *J*= 8.6 Hz, C_{Ar}2, C_{Ar}6-H), 7.73 (2H, d, *J*= 8.6 Hz, C_{Ar}3, C_{Ar}5-H), 8.51 (1H, d, *J*= 7.9 Hz, C7-H); MS m/z: 452 (M^+); *Anal*. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.04; H, 5.20; N, 6.20; IR (KBr) cm^{-1}: 1642 (NC=O), 1596 (C=C), 1520, 1346 (NO_2).

(2,3-Dimethyl-1*H*-indol-1-yl)(4-nitrophenyl)methanone (5a) Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.22 (3H, s, C3-Me), 2.30 (3H, s, C2-Me), 6.96 (1H, d, *J*= 8.4 Hz, C4-H), 7.04 (1H, dd, *J*= 8.1, 8.4 Hz, C5-H), 7.19 (1H, dd, *J*= 7.7, 8.1 Hz, C6-H), 7.43 (1H, d, *J*= 7.7 Hz, C7-H), 7.83 (2H, d, *J*= 8.8 Hz, C_{Ar}2, C_{Ar}6-H), 8.31 (2H, d, *J*= 8.8 Hz, C_{Ar}3, C_{Ar}5-H); MS m/z: 294 (M^+); IR (film) cm^{-1}: 1684 (NC=O), 1602 (C=C), 1522, 1342 (NO_2).

(4-Chlorophenyl)[2-(2-methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl]methanone (9b) (*syn)* Colorless prisms from EtOH; mp 181-182 °C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.97 (3H, s, C3-Me), 1.58 (3H, s, C3-Me), 3.66 (3H, s, C_{naph}2-OMe), 6.16 (1H, s, C2-H), 6.58-7.71 (13H, m, aromatic C-H), 8.47 (1H, br s, C7-H); MS m/z: 441 (M^+); *Anal*. Calcd for $C_{28}H_{24}ClNO_2$: C, 76.08; H, 5.48; N, 3.17. Found: C, 75.67; H, 5.41; N, 3.44; IR (KBr) cm^{-1}: 1642 (NC=O), 1596 (C=C).

(4-Chlorophenyl)[2-(2-methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl]methanone (10b) (*anti)* Colorless needles from EtOH; mp 169-170 °C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.98 (3H, s, C3-Me), 1.61 (3H, s, C3-Me), 3.44 (3H, s, C_{naph}2-OMe), 5.82 (1H, s, C2-H), 6.70-7.73 (13H, m, aromatic C-H), 8.37 (1H, br s, C7-H); MS m/z: 441 (M^+); *Anal*. Calcd for $C_{28}H_{24}ClNO_2$: C, 76.08; H, 5.48; N, 3.17. Found: C, 76.04; H, 5.45; N, 3.19; IR (KBr) cm^{-1}: 1620 (NC=O), 1592 (C=C).

[2-(2-Methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](phenyl)methanone (9c) (*syn*) Colorless prisms from EtOH; mp 145-147 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.97 (3H, s, C3-Me), 1.59 (3H, s,

C3-Me), 3.58 (3H, s, C_{naph}2-OMe), 6.23 (1H, br s, C2-H), 6.65-7.70 (14H, m, aromatic C-H), 8.52 (1H, br s, C7-H); MS m/z: 407 (M^+); *Anal*. Calcd. for $C_{28}H_{25}NO_2$: C, 82.53; H, 6.18 ; N, 3.44. Found: C, 82.33; H, 6.13; N, 3.43; IR (KBr) cm^{-1}: 1638 (NC=O), 1594 (C=C).

[2-(2-Methoxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](phenyl)methanone (10c) (*anti*) Colorless prisms from EtOH; mp 185-187 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.95 (3H, s, C3-Me), 1.62 (3H, s, C3-Me), 3.46 (3H, s, C_{naph}2-OMe), 5.90 (1H, br s, C2-H), 6.65-7.70 (14H, m, aromatic C-H), 8.41 (1H, br s, C7-H); MS m/z: 407 (M^+); *Anal*. Calcd. for $C_{28}H_{25}NO_2$: C, 82.53 ; H, 6.18 ; N, 3.44. Found: C, 82.33; H, 6.13 ; N, 3.43. IR (KBr) cm^{-1}: 638 (NC=O), 1594 (C=C).

Single Crystal X-Ray Analysis of 8aa A colorless prismatic crystal having approximate dimensions of 0.10 x 0.20 x 0.10 mm of **8aa** was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R four-circle autodiffractometer with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 20 ± 1 °C to a maximum 2θ value of 55.0°. The structure was solved by direct method (SIR-92[7]), 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[7] crystallographic software package.

Crystal Data of **8aa**: Crystal Data; $C_{27}H_{22}N_2O_4$, M=438.47, monoclinic, Space group $P2_1/a$, a=12.281 (2), b=20.134 (5), c=9.854 (1) Å, β =111.39 (1), V=2268 (7) $Å^3$, Dc=1.284 g cm^{-3}, Z=4, R=0.057, Rw=0.094. The X-Ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC ref. No. 702823).

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REFERENCES (AND NOTES)

1. a) K. Harano, M. Yasuda, Y. Ida, T. Komori, and T. Taguchi, *Cryst. Struc. Commun.*, 1981, **10**, 165. b) M. Eto, K. Harano, T. Hisano, and T. Kitamura, *J. Heterocycl. Chem.*, 1992, **29**, 311. c) T. Kitamura, K. Harano, and T. Hisano, *Chem. Pharm. Bull.*, 1992, **40**, 2255. d) M. Eto, F. Ito, T. Kitamura, and K. Harano, *Heterocycles*, 1994, **38**, 2159. e) M. Eto, F. Ito, T. Kitamura, and K. Harano, *Heterocycles*, 1996, **43**, 1159. f) A. Watanabe, M. Moriguchi, F. Ito, Y. Yoshitake, M. Eto, and K. Harano, *Heterocycles*, 2000, **53**, 1. g) F. Ito, T. Moriguchi, Y. Yoshitake, M. Eto, S. Yahara, and K. Harano, *Chem. Pharm. Bull.*, 2003, **51**, 688. h) A. Watanabe, K. Yamaguchi, F. Ito, Y. Yoshitake, and K. Harano, *Heterocycles*, 2007, **71**, 343.

2. a) M. Oki, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 87. b) M. Oki, 'Topics in Stereochemistry', Vol. 14, ed. by N. L. Allinger, E. L. Eliel, and S. H. Wilen, John Wiley & Sons, New York, 1983, pp 47-79. c) M. Oki, *Acc. Chem. Res.*, 1990, **23**, 351.
3. C. K. Johnson, ORTEP ORNL-3794, Oak Ridge National Laboratory, Tennessee, U. S. A., 1965.
4. a) R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063. b) G. R. Desiraju, *Acc. Chem. Res.*, 1991, **24**, 290. c) T. Steiner, J. A. Kanters, and J. A. Kroon, *J. Chem. Soc., Chem. Commun.*, 1996, 1277. d) Y. Gu, T. Kar, and S. Scheiner, *J. Am. Chem. Soc.*, 1999, **121**, 9411.
5. J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms and Structure', McGraw Hill, 1968, pp 429.
6. a) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902. b) J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 209. c) J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 221. d) WinMOPAC V3.9, Fujitsu Ltd, Tokyo, 2004.
7. a) SIR92: A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.*, 1994, **27**, 435. b) Crystal Structure 3.6.0: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC, USA, 2000-2004. c) CRYSTALS Issue 10: D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge, Chemical Crystallography Laboratory, Oxford, UK., 1996.