Modern Friedel-Crafts chemistry. Part 35. New synthetic approach to substituted indolo[2,1-*a*][2]benzazepines and indolo[2,1-*a*]isoquinolines via Friedel-Crafts cyclialkylations

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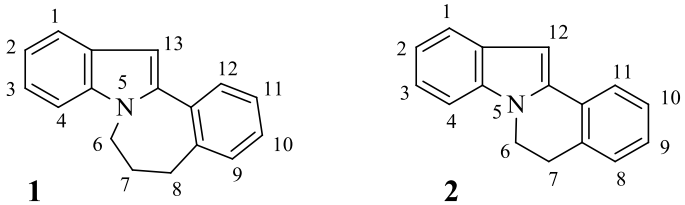
Abstract

Facile procedures for the construction of fused indole-containing heteropolycycles **1a-f** and **2a-c** have been developed. The methodology involves Friedel-Crafts cyclialkylations of heteoraryl alkanols in the presence of both Brönsted (PPA) and Lewis ($AlCl_3/CH_3NO_2$) acid catalysts. The starting alkanols **6a-f** and **12a-c** were smoothly obtained both by reactions of the corresponding carboxylic acid esters and the corresponding ketones with Grignard reagents. Overall, this approach allows for easy and efficient access to polycyclic indoles from easily synthesized precursors.

Keywords: Friedel-Crafts cyclialkylation, heteropolycycles, 7-methyl-2-phenyl-1*H*-indole, heteroarylalkanols, Grignard reagents, 5,6-dihydro-8-methylindolo[2,1-*a*]isoquinoline

Introduction

Heteropolycycles containing indole moieties possess a wide diversity of biological activities[1] beside their presence in a large array of pharmaceuticals[2] and natural products.[3] For example, 7,8-dihydro-6*H*-indolo[2,1-*a*][2]benzazepine (**1**)[4] and 6,7-dihydroindolo[2,1-*a*]isoquinoline (**2**)[5-7] have unique nitrogen-containing tetracyclic[8] structures (Scheme 1). Their analogues occur widely in isolated natural products[9], in drugs[10] and the derived π-conjugated materials are used as organic semiconductors.[11]



1 **2**

Scheme 1. Indole scaffolds containing heteropolycycles.

The indole scaffold **1** was obtained early by Kozikowski *et al*.[12,13] from the derived *N*-alkylindole and 2-bromobenzyl bromide in the presence of $Pd(PPh_3)_4$. Lee and co-workers[14,15] reported the synthesis of benzazepinoindoles via intramolecular Heck type reaction by applying intramolecular palladium-catalyzed arylation of indole-containing Baylis–Hillman adducts.[16] Orito *et al.*[17] reported the formation of alkaloids of berberine and dibenzopyrrocoline series via the palladium-catalyzed coupling of amide derived from *o*-halobenzylisoquinolines. On the other hand, Sharma *et al*.[18] reported interesting examples for the synthesis of benzazepinoindoles through the 7-endo *trig* Pictet-Spengler cyclization with various carbonyl compounds.[19]

Other strategies have been successfully applied in the synthesis of polyindoles. That included benzyne reactions[20], oxidative couplings of 1-benzylisoquinoline[21], enamine photocyclization[22], silicon mediated ring closure of benzyl anion[23], radical cyclization[24] and palladium-catalyzed couplings.[25]

Faust *et al*.[5] failed to prepare the tetracyclic amine indoloisoquinoline (**2**) by the methodology of Kozikowski. However, they succeeded to obtain **2** via consecutive six-step reactions starting from 3-formylindoles in low overall yields. Other synthetic methodologies have been developed to generate these compounds by stepwise introduction or construction of the pyrrole and benzene rings.[26]

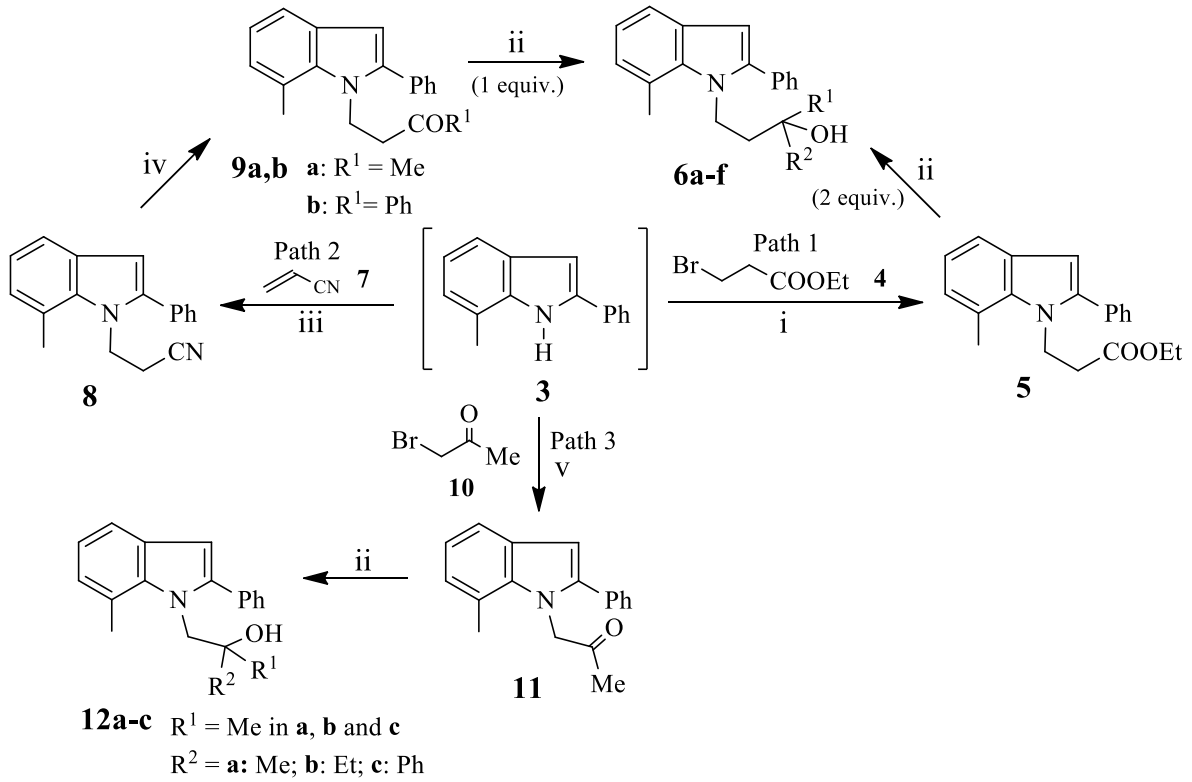
The development of new direct, concise and economical routes to this class of compound is currently a popular research area for both medicinal and synthetic organic chemists.[27,28] In this paper, we applied our experience in Friedel-Crafts cyclialkylations[29-36] to offer unequivocal syntheses for both substituted 7,8-dihydro-6*H*-indolo[2,1-*a*][2]benzazepine (**1**) and 6,7-dihydro-indolo[2,1-*a*]isoquinoline (**2**) via intramolecular ring closures of some synthesized heteroaryl alkanols.

Results and Discussion

Synthesis of cyclialkylating alcohols

The heteroaryl alkanols required for this work (**6a-f** and **12a-c)** were all obtained starting from the easily accessible[37] 7-methyl-2-phenyl-1*H*-indole (**3)** via three different pathways as formulated in Scheme 2: Path 1, included the base catalyzed N-alkylation of **3** with ethyl 3-bromopropanoate (**4**) to give ethyl 3-(7-methyl-2-phenyl-1*H*-indol-1-yl)propanoate (**5**). This ester was allowed to react with two equivalents of Grignard reagents[38-40] to afford the corresponding tertiary alcohols **6a-c** ($R^1 = R^2$) (Table 1, Entries 1-3).

Path 2 comprised the conversion of substrate **3** to tertiary alcohols **6d-f** via three consecutive steps: (i) cyanoethylation[41] of **3** with acrylonitrile (**7**) in the presence of Triton B, (ii) reaction of the resulting nitrile **8** with one equivalent of Grignard reagents to afford ketones **9a,b** and (iii) reaction of ketones **9a,b** with Grignard reagents to give alcohols **6d-f** ($R^1 \# R^2$) (Table 1, Entries 4-6).



Scheme 2. Reagents and conditions: (i) K_2CO_3/Cu, xylene, reflux 12 h, 85%, (ii) RMgX, Et_2O, NH_4Cl soln, (Table 1), (iii) Triton B, dioxane, 80-90°C, 5 h, 75%, (iv) RMgX, Et_2O/PhH, HCl, reflux, (v) K_2CO_3/KI, acetone, 10 h, 78%.

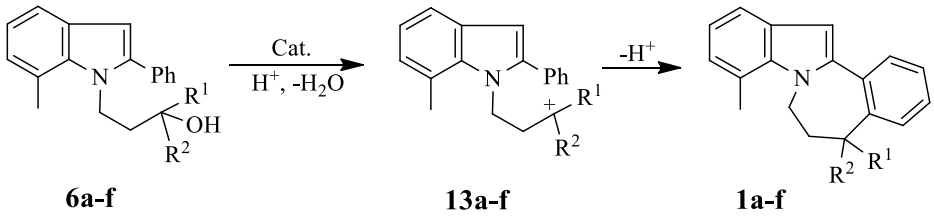
Table 1. Optimum conditions for the synthesis of heteroarylalkanols **6a-f** and **12a-c**

Entry	Substrate	R^1	R^2	Conditions[a]	Mp °C (n_D^{25})	Product (%)[b]
1	**5**	Me	Me	MeMgI, Et_2O, rt, 8hr	110	**6a** (87)
2	**5**	Et	Et	EtMgBr, Et_2O, rt, 8hr	83	**6b** (84)
3	**5**	Ph	Ph	PhMgBr, Et_2O, rt, 15hr	142	**6c** (79)
4	**9a**	Me	Et	EtMgBr, Et_2O, rt, 9hr	92	**6d** (91)
5	**9b**	Ph	Et	EtMgBr, Et_2O, rt, 13hr	120	**6e** (82)
6	**9a**	Me	Ph	PhMgBr, Et_2O, rt, 10hr	98	**6f** (86)
7	**11**	Me	Me	MeMgI, Et_2O, rt, 8hr	68	**12a** (92)
8	**11**	Me	Et	EtMgBr, Et_2O, rt, 9hr	(1.568)	**12b** (89)
9	**11**	Me	Ph	PhMgBr, Et_2O, 15hr	(1.584)	**12c** (85)

[a]All reactions were performed using 0.2 equiv. excess of RMgX. [b]Isolated yield refer to substrate.

The third route (path 3) encompassed the production of alcohols **12a-c**. These were prepared smoothly through the N-alkylation of **3** with 1-bromopropan-2-one (**10**) to give 1-(7-methyl-2-phenyl-1*H*-indol-1-yl)propan-2-one (**11**). The latter ketone was treated with Grignard reagents to afford alcohols **12a-c** (Scheme 2, Table 1, Entries 7-9). The structures of all new alcohols were appropriately established by the usual spectroscopic methods.

Cyclialkylations producing substituted 7,8-dihydro-6*H*-indolo[2,1-*a*][2]benzazepines (1a-f). Cyclialkylations of alcohols **6a-f** were conducted in the presence of $AlCl_3/CH_3NO_2$ and PPA catalysts under the conditions outlined in Table 2 to give the title benzazepines **1a-f** (Table 2 and Scheme 3).



Scheme 3. Cyclialkylations of heteroarylalkanols **6a-f**.

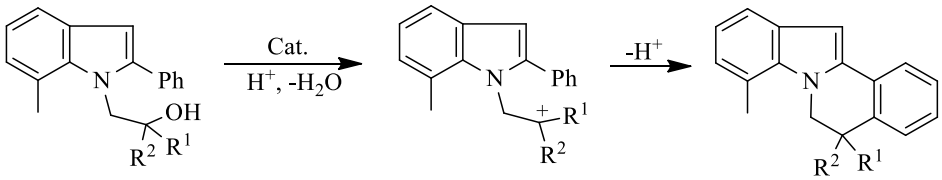
Table 2. Cyclialkylation conditions and results of heteroarylalkanols **6a-f**

Entry	Substrate	Catalyst	Solvent	Temp. °C	Time (h)	Product (%)[a]
1	**6a**	$AlCl_3/CH_3NO_2$[b]	DCM[c]	RT	2	**1a** (82)
2	**6a**	PPA[d]	--	160	2	**1a** (75)
3	**6b**	$AlCl_3/CH_3NO_2$	DCM	RT	2	**1b** (81)
4	**6b**	PPA	--	160	1	**1b** (73)
5	**6c**	$AlCl_3/CH_3NO_2$	DCM	50	52	**1c** (81)
6	**6c**	PPA	--	220	14	**1c** (76)
7	**6d**	$AlCl_3/CH_3NO_2$	DCM	RT	2	**1d** (79)
8	**6d**	PPA	--	160	2	**1d** (74)
9	**6e**	$AlCl_3/CH_3NO_2$	DCM	RT	2	**1e** (84)
10	**6e**	PPA	--	160	2	**1e** (74)
11	**6f**	$AlCl_3/CH_3NO_2$	DCM	RT	4	**1f** (80)
12	**6f**	PPA	--	160	2	**1f** (76)

[a]Isolated yield refer to substrate. [b]With $AlCl_3/CH_3NO_2$ catalyst reactant proportions were: carbinol (0.002 mole), $AlCl_3$ (0.0024 mole), CH_3NO_2 (0.024 mole), solvent (10 ml). [c]Dichloromethane. [d]With PPA catalyst reactant proportions were: carbinol (0.5 g) and PPA (5 g).

Cyclialkylation of alcohol **6c** (R^1, R^2 = Ph) to 7,8-dihydro-4-methyl-8,8-diphenyl-6*H*-indolo[2,1-*a*][2]benzazepines (**1c**) was effected in the presence of acidic catalysts under more strenuous conditions. As evident from Table 2 (Entries 5 and 6), cyclialkylation of **6c** with $AlCl_3/CH_3NO_2$ required 52 h in DCM solution at 50°C and with PPA required 14 h at 220 °C. That was attributed to the steric interactions exerted by both bulky phenyl groups at the closure step.[29-35]

Cyclialkylations producing substituted 6,7-dihydroindolo[2,1-*a*]isoquinolines (2a-c). Cyclialkylations of alcohols **12a-c** were smoothly carried out in the presence of $AlCl_3/CH_3NO_2$ and PPA catalysts under different reaction conditions (Table 3, Scheme 4). Upon treatment of such alcohols with acidic catalysts, the generated stable tertiary carbocations **14a-c** underwent closure to substituted 6,7-dihydroindolo[2,1-*a*]isoquinoline **2a-c** in overall high reaction yields.



12a-c **14a-c** **2a-c**

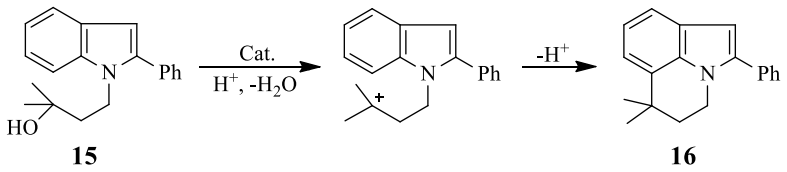
Scheme 4. Cyclialkylations of heteroarylalkanols **12a-c**.

Table 3. Cyclialkylation conditions and results of heteroarylalkanols **12a-c**

Entry	Substrate	Catalyst	Solvent	Temp. °C	Time (h)	Product (%)
1	**12a**	$AlCl_3/CH_3NO_2$	DCM	RT	3	**2a** (82)
2	**12a**	PPA	--	140	1	**2a** (76)
3	**12b**	$AlCl_3/CH_3NO_2$	DCM	RT	3	**2b** (85)
4	**12b**	PPA	--	140	1.5	**2b** (73)
5	**12c**	$AlCl_3/CH_3NO_2$	DCM	RT	5	**2c** (79)
6	**12c**	PPA	--	160	1	**2c** (78)

Before closing this discussion, it is worthwhile to contrast the results of this work in which the cyclialkylating substrates (**6a-f** and **12a-c**) include a 7-methyl-2-phenyl-1*H*-indol-1-yl moiety with a previous case[36] in which the 7-methyl was missing. In the present work, electrophilic ring closure occurred exclusively at the 2-phenyl group yielding either benzazepine or isoquinoline derivatives. In the previous case, however, closure occurred at the 7-position (which is not blocked) to yield the respective quinoline derivative (Scheme 5). That proofs, however, that attack on the 7-position of the indolyl moiety, if not blocked, is favored over attack on the phenyl group that is attached to the 2-position of the indolyl moiety. Moreover, the fact that the ^1H

NMR chemical shift of the methyl group remained nearly constant suggests that *ipso*-substitution is not involved.



Scheme 5. Literature conversion of 2-methyl-4-(2-phenyl-1*H*-indol-1-yl)butan-2-ol (**15**) to 6,6-dimethyl-2-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (**16**).

Conclusions

We have developed new, simple and facile synthetic pathways for the construction of different indole-based substituted heteropolycycles via Friedel-Crafts cyclialkylation of heteroarylalkanols (**6a-f** and **12a-c)** catalyzed by $AlCl_3/CH_3NO_2$ and PPA. To the best of our knowledge, this is the first time that such novel substituted tetracycles (**1a-f** and **2a-c)** have been described. The results show Friedel-Crafts cyclialkylations to be useful pathways to the syntheses of heteropolycycles.

Experimental Section

General. Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus. The IR spectra were determined with a Shimadzu 470 Infrared spectrophotometer using KBr wafer and thin film techniques (ν cm^{-1}). The ^1H NMR spectra were recorded by JEOL LA 400 MHz FT-NMR (400 MHz) and Varian 90 MHz NMR spectrometer using $CDCl_3$ solvent with TMS as internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. The mass spectra were performed by JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. The refractive index was measured using a Schmidt Haensch apparatus. Reactions were monitored by thin layer chromatography (TLC) using precoated silica plates visualized with UV light. Flash column chromatography was performed on basic alumina (E. Merck) with suitable eluents.

Ethyl 3-(7-methyl-2-phenyl-1*H*-indol-1-yl)propanoate (**5**). A mixture of 7-methyl-2-phenyl-1*H*-indole **3** (4.1 g, 20 mmol), ethyl 3-bromopropanoate **4** (5 g, 3.4 mL, 28 mmol), anhydrous K_2CO_3 (1.6 g, 12 mmol) and a catalytic amount of Cu-metal (0.3 g) in xylene (25 mL) was refluxed for 12 h. Afterwards the solvent was removed by steam distillation and the residue was

diluted with water and extracted with ether (3 × 40 mL). The combined ethereal extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated to give crude oily ester (5.2 g, 85.5%). Purification by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) gave pure ethyl 3-(7-methyl-2-phenyl-1*H*-indol-1-yl)propanoate (**5**) (4.9 g, 80.6%) as a pale yellow oil; n_D^{25} 1.571. IR (film) ν_{max} 3050, 2985, 1745, 1600, 1560, 1490, 1455, 1320, 1170, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.30 (3H, t, *J* 9.0 Hz, CH_3), 2.20 (3H, s, CH_3), 2.70 (2H, s, *J* 9.0 Hz, CH_2), 4.10 (2H, t, *J* 7.5 Hz, CH_2), 4.30 (2H, t, *J* 7.5 Hz, CH_2), 6.50 (1H, s, CH) and 6.90-7.70 ppm (8H, m, Ar-H); Anal. Calcd. for $C_{20}H_{21}NO_2$ (307); C, 78.17; H, 6.84; N, 4.56. Found; C, 78.20; H, 6.88; N, 4.23%.

3-(7-Methyl-2-phenyl-1*H*-indol-1-yl)propanenitrile (8). To an ice-cold solution of 7-methyl-2-phenyl-1*H*-indole **3** (5.1 g, 25 mmol) and acrylonitrile **7** (4 g, 5 mL, 75 mmol) in dioxane (20 mL) was treated with 0.5 ml of Triton B. The reaction mixture was heated in a steam bath at 80-90 °C for 5 h and then it was concentrated. The residue was triturated with methanol (3 × 5 mL) and the solid product was filtered off, washed copiously with water, and dried to give crude nitrile (4.8 g, 75%). Crystallization from acetone gave pure nitrile **8** (4.3 g, 67%) as white crystals, mp 102 °C. IR (KBr): ν_{max} 3070, 2985, 2250, 1580, 1475, 1450, 1320, 1175, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.30 (3H, s, CH_3), 2.80 (2H, t, *J* 7.5 Hz, CH_2), 4.20 (2H, t, *J* 7.5 Hz, CH_2), 6.50 (1H, s, CH) and 6.90-7.70 (8H, m, Ar-H);Anal. Calcd. for $C_{18}H_{16}N_2$ (260); C, 83.07; H, 6.15; N, 10.76. Found; C, 82.75; H, 6.2; N, 10.93%.

Synthesis of heteroaryl ketones 9a,b. General procedure

To an ice-cold Grignard reagent obtained as usual[40] from Mg turnings (0.24 g, 10 mmol), alkyl or aryl halide (10 mmol) in ether (30 mL) was added with stirring a solution of nitrile **8** (2 g, 8 mmol) in benzene (30 mL) over 10 min. After complete addition, the solution was refluxed for 10 hr then it was poured with srirring into ice-cold hydrochloric acid (100 mL, 30%). The organic solvent was evaporated and the mixture was concentrated. The resulted mixture was then hydrolyzed by refluxing with a mixture of (benzene, 20 mL and HCl, 10 mL) for 10 h. The solution was cold and benzene layer was separated, while the aqueous layer was basified by vertually addition of solid Na_2CO_3 with stirring and then extracted with benzene (2×30 mL). The combined benzene extracts were washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed to afford the crude ketones **9a,b** which were purified by crystallization. The spectral data of the ketones **9a,b** are given below.

4-(7-Methyl-2-phenyl-1*H*-indol-1-yl)butan-2-one (**9a**). Yield 82%; mp 73°C (ethanol); IR (KBr) ν_{max} 3060, 2975, 1745, 1580, 1485, 1450, 1365, 1285, 1070, 1030, 750, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.10 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.80 (2H, t, *J* 7.5 Hz, CH_2), 4.10 (2H, t, *J* 7.5 Hz, CH_2), 6.50 (1H, s, CH) and 6.80-7.60 (8H, m, Ar-H); Anal. Calcd. for $C_{19}H_{19}NO$ (277); C, 82.31; H, 6.85; N, 5.05. Found; C, 81.90; H, 6.70; N, 5.15%.

3-(7-Methyl-2-phenyl-1*H*-indol-1-yl)-1-phenylpropan-1-one (**9b**): Yield 88%; mp 102 °C (methanol). IR (KBr) ν_{max} 3070, 2980, 1705, 1570, 1475, 1455, 1370, 1060, 1030, 735 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.20 (3H, s, CH_3), 2.90 (2H, t, *J* 7.5 Hz, CH_2), 4.0 (2H, t, *J* 7.5

Hz, CH_2), 6.50 (1H, s, CH) and 6.80-7.50 (13H, m, Ar-H); Anal. Calcd. for $C_{24}H_{21}NO$ (339); C, 84.95; H, 6.19; N, 4.12. Found; C, 84.77; H, 6.30; N, 4.43%.

Synthesis of 1-(7-methyl-2-phenyl-1*H*-indol-1-yl)propan-2-one (**11**)

To a stirred mixture of compound **3** (4.1g, 20 mmol), anhydrous K_2CO_3 (1.6 g, 12 mmol) and a catalytic amount of potassium iodide (0.2 g) in dry acetone (30 mL) was added dropwise a solution of bromoacetone **10** (3.8g, 28 mmol) in dry acetone (20 mL) at reflux temperature. Reflux was continued for 10 h. The reaction mixture was concentrated to dryness and then transferred to ice water (100 mL). The separated solid was collected by filtration and crystallized from acetone to yield ketone **11** (4 g, 78%) as faint yellow crystals, m p 118°C. IR (KBr) ν_{max} 3070, 3015, 2985, 1745, 1580, 1470, 1440, 1370, 1060, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.10 (3H, s, CH_3), 2.40 (3H, s, CH_3), 4.90 (2H, s, CH_2), 6.60 (1H, s, CH) and 6.90-7.90 (8H, m, Ar-H); Anal. Calcd. for $C_{18}H_{17}NO$ (263); C, 82.12; H, 6.46; N, 5.32. Found; C, 81.85; H, 6.42; N, 5.40%.

Synthesis of alcohols 6a-f and 12a-c. General procedure

To an ice-cold Grignard reagent solution obtained as usual[38,39] from Mg turnings (0.2 g, 8 mmol), alkyl-or aryl halide (8 mmol) in ether (25 mL), was added a solution of ester **5** (1 g, 3.3 mmol) and/or ketones **9a,b** or **11** (6.6 mmol) in ether (30 mL). the reaction mixture was stirred at required temperature for appointed time (Table 1) followed by decomposition with sat. aq.NH_4Cl soln. The product was extracted with ether (3×30 mL) and the combined organic phases were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) gave the pure product **6a-f** and **12a-c**. The conditions and yields are shown in Table 1 and spectral data are given below:

2-Methyl-4-(7-methyl-2-phenyl-1*H*-indol-1-yl)butan-2-ol (**6a**). White crystals, mp 110 ºC (methanol). IR (KBr) ν_{max} 3385, 3080, 2960, 2850, 1580, 1470, 1450, 1440, 1330, 915, 750, 670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.20 (6H, s, $2CH_3$), 1.90 (2H, t, *J* 7.5 Hz, CH_2), 2.20 (3H, s, CH_3), 3.10 (1H, s, OH exchangeable with D_2O), 3.70 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 7.0-8.0 (8H, m, Ar-H); Anal. Calcd. for $C_{20}H_{23}NO$ (293); C, 81.91; H, 7.85; N, 4.77. Found; C, 81.57; H, 8.20; N, 4.95%.

3-Ethyl-1-(7-methyl-2-phenyl-1*H*-indol-1-yl)pentan-3-ol (**6b**). White plates, mp 83 ºC (ethanol). IR (KBr) ν_{max} 3420, 3070, 2950, 1600, 1580, 1470, 1450, 1330, 750, 675 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.90 (6H, t, *J* 9.0 Hz, $2CH_3$), 1.40 (4H, m, *J* 9.0 Hz, $2CH_2$), 1.90 (2H, t, *J* 7.5 Hz, CH_2), 2.10 (1H, s, OH exchangeable with D_2O), 2.20 (3H, s, CH_3), 3.70 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.80-7.90 (8H, m, Ar-H); Anal. Calcd. for $C_{22}H_{27}NO$ (321); C, 82.24; H, 8.41; N, 4.36. Found; C, 82.50; H, 8.37; N, 4.70%.

3-(7-Methyl-2-phenyl-1*H*-indol-1-yl)-1,1-diphenylpropan-1-ol (**6c**). White crystals, mp 142 ºC (methanol). IR (KBr) ν_{max} 3370, 3090, 2910, 1610, 1585, 1475, 1440, 1330, 755, 670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.30 (3H, s, CH_3), 2.50 (1H, s, OH exchangeable with D_2O),

2.60 (2H, t, *J* 7.5 Hz, CH_2), 3.90 (2H, t, *J* 7.5 Hz, CH_2), 6.70 (1H, s, CH) and 7.10-7.90 (18H, m, Ar-H); Anal. Calcd. for $C_{30}H_{27}NO$ (417); C, 86.33; H, 6.47; N, 3.35. Found; C, 86.37; H, 6.62; N, 3.25%.

3-Methyl-1-(7-methyl-2-phenyl-1*H*-indol-1-yl)pentan-3-ol (**6d**). White crystals, mp 92 ºC (ethanol). IR (KBr) ν_{max} 3385, 3090, 2990, 1600, 1590, 1480, 1460, 1440, 1330, 760, 675 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.80 (3H, t, *J* 9.0 Hz, CH_3), 1.30 (3H, s, CH_2), 1.40 (2H, q, *J* 9.0 Hz, CH_2), 1.70 (1H, s, OH exchangeable with D_2O), 2.20 (3H, s, CH_3), 1.80 (2H, t, *J* 7.5 Hz, CH_2), 3.70 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.80-7.90 (8H, m, Ar-H); Anal. Calcd. for $C_{21}H_{25}NO$ (307); C, 82.08; H, 8.14; N, 4.56. Found; C, 82.42; H, 8.09; N, 4.28%.

1-(7-Methyl-2-phenyl-1*H*-indol-1-yl)-3-phenylpentan-3-ol (**6e**). Pale yellow needles, mp 120 ºC (1:3 benzene/ PE 60-80 ºC). IR (KBr) ν_{max} 3340, 3080, 2985, 1615, 1570, 1470, 1460, 1445, 1330, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.90 (3H, t, *J* 9.0 Hz, CH_3), 1.70 (2H, q, *J* 9.0 Hz, CH_3), 2.10 (2H, t, *J* 7.5 Hz, CH_2), 2.20 (1H, s, OH exchangeable with D_2O), 2.30 (3H, s, CH_3), 3.80 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.80-7.90 (13H, m, Ar-H); Anal. Calcd. for $C_{26}H_{27}NO$ (369); C, 84.55; H, 7.04; N, 3.94. Found; C, 84.82; H, 7.36; N, 4.27%.

4-(7-Methyl-2-phenyl-1*H*-indol-1-yl)-2-phenylbutan-2-ol (**6f**). White plates, mp 98 ºC (ethanol). IR (KBr) ν_{max} 3360, 3090, 2970, 1600, 1580, 1450, 1440, 1330, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.50 (3H, s, CH_3), 2.20 (2H, t, *J* 7.5 Hz, CH_2), 2.30 (3H, s, CH_3), 2.50 (1H, s, OH exchangeable with D_2O), 3.80 (2H, t, *J* 7.5 Hz, CH_2), 6.70 (1H, s, CH) and 6.80-8.0 (13H, m, Ar-H); Anal. Calcd. for $C_{25}H_{25}NO$ (355); C, 84.50; H, 7.04; N, 3.94. Found; C, 84.57; H, 7.20; N, 3.75%.

2-Methyl-1-(7-methyl-2-phenyl-1*H*-indol-1-yl)propan-2-ol (**12a**). White needles; mp 68 °C (1:3 benzene/PE 60-80 °C). IR (KBr) ν_{max} 3370 , 3090, 2965, 1590, 1480, 1460, 1450, 1345, 1030, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.20 (6H, s, $2CH_3$), 2.30 (3H,s, CH_3), 2.60 (1H, s, OH exchangeable with D_2O), 4.0 (2H, t, *J* 7.5 Hz, CH_2), 6.50 (1H, s, CH) and 6.80-8.10 (8H, m, Ar-H); Anal. Calcd. for $C_{19}H_{21}NO$ (279); C, 81.72; H, 7.52; N, 5.01; Found; C, 81.53; H, 7.33; N, 5.17%.

2-Methyl-1-(7-methyl-2-phenyl-1*H*-indol-1-yl)butan-2-ol (**12b**). Reddish viscous oil; n_D^{25} 1.568. IR (film) ν_{max} 3450 , 3085, 2970, 1600, 1480, 1460, 1450, 1345, 1020, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.90 (3H, t, *J* 9.0 Hz, CH_3), 1.30 (3H, s, CH_3), 1.40 (2H, t, *J* 9.0 Hz, CH_2), 1.70 (1H, s, OH exchangeable with D_2O), 2.30 (3H,s, CH_3), 3.80-4.10 (2H, m, *J* 6.0 Hz, CH_2), 6.60 (1H, s, CH) and 6.90-8.0 (8H, m, Ar-H); Anal. Calcd. for $C_{20}H_{23}NO$ (293); C, 81.91; H, 7.84; N, 4.77; Found; C, 81.75; H, 8.24; N, 4.79%.

1-(7-Methyl-2-phenyl-1*H*-indol-1-yl)-2-phenylpropan-2-ol (**12c**). Pale yellow viscous oil; n_D^{25} 1.584. IR (film) ν_{max} 3450 , 3085, 2970, 1600, 1480, 1460, 1450, 1345, 1020, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.60 (3H, s, CH_3), 2.30 (3H, s, CH_3), 1.40 (1H, s, OH exchangeable with D_2O), 4.20-4.40 (2H, m, *J* 6.0 Hz, CH_2), 6.50 (1H, s, CH) and 6.80-8.0 (13H, m, Ar-H); Anal. Calcd. for $C_{24}H_{23}NO$ (341); C, 84.45; H, 6.74; N, 4.10; Found; C, 84.38; H, 6.79; N, 4.37%.

Cyclialkylation procedures

The procedures described earlier for cyclialkylation of arylalkanols with $AlCl_3/CH_3NO_2$[30] and PPA[31] were essentially followed. Purification of the crude isolated products with flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) gave the pure product. The conditions and yields for the products **1a-f** and **2a-c** are shown in Tables 2 and 3 while the physical constants and spectral data of the products are given below.

7,8-Dihydro-4,8,8-trimethyl-6*H*-indolo[2,1-*a*][2]benzazepine (**1a**). Reddish viscous oil; n_D^{25} 1.566; R_f 0.35 (1:3 EtOAc/hexane). IR (film) ν_{max} 3075, 2985, 1600, 1565, 1490, 1445, 1430, 1330, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.30 (6H, s, $2CH_3$), 2.0 (2H, t, *J* 7.5 Hz, CH_2), 2.30 (3H, s, CH_3), 3.70 (2H, t, *J* 7.5 Hz, CH_2), 6.50 (1H, s, CH) and 6.80-7.92 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 276 (M^++1, 44.8), 275 (M^+, 9.5), 274 (M^+–H, 82.5), 260 (M^+–CH_3, 100), 245 (51.2), 230 (M^+–$3CH_3$, 21.5), 206 (15.3), 192 (8.3), 178 (5.6), 166 (10.3), 151 (2.4), 109 (3.7), 91 (1.8), 77 (5.5); Anal. Calcd. for $C_{20}H_{21}N$ (275): C, 87.27; H, 7.63; N, 5.09. Found: C, 87.37; H, 7.85; N, 4.68%.

8,8-Diethyl-7,8-dihydro-4-methyl-6*H*-indolo[2,1-*a*][2]benzazepine (**1b**). Pale yellow plates mp 90 °C (benzene); R_f 0.42 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3075, 2980, 1610, 1570, 1490, 1445, 1430, 1330, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.90 (6H, t, *J* 9.0 Hz, $2CH_3$), 1.50 (2H, m, *J* 9.0 Hz, $2CH_2$), 2.0 (2H, t, *J* 7.5 Hz, CH_2), 2.30 (3H,s, CH_3), 3.70 (2H, m, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.90-8.0 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 203 (M^+, 7.5), 302 (M^+–H, 100), 288 (M^+–CH_3, 18.2), 274 (40.5), 272 (M^+–$2CH_3$–H, 45.2), 245 (M^+–$2C_2H_5$, 11.8), 230 (M^+–$2C_2H_5$–CH_3, 17.4), 206 (11.4), 192 (7.8), 179 (4.1), 166 (9.4), 151 (1.5), 109 (6.2), 91 (2.4), 77 (5.8); Anal. Calcd. for $C_{22}H_{25}N$ (303): C, 87.12; H, 8.25; N, 4.62. Found: C, 87.25; H, 8.09; N, 4.76%.

7,8-Dihydro-4-methyl-8,8-diphenyl-6*H*-indolo[2,1-*a*][2]benzazepine (**1c**). White plates, mp 138 °C (benzene); R_f 0.2 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3090, 2976, 1605, 1590, 1480, 1450, 1425, 1330, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.30 (3H,s, CH_3), 2.70 (2H, t, *J* 7.5 Hz, CH_2), 3.90 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.90-8.20 (17H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 399 (M^+, 4.8), 398 (M^+–H, 85.5), 384 (M^+–CH_3, 32.4), 383 (18.6), 322 (M^+–Ph, 51.4), 245 (20.6), 230 (M^+–2Ph–CH_3, 22.7), 206 (8.3), 192 (6), 178 (2.1), 166 (6.2), 151 (2.3), 109 (9.4), 91 (5.4), 77 (7.4); Anal. Calcd. for $C_{30}H_{25}N$ (399): C, 90.22; H, 6.26; N, 3.50 Found: C, 90.25; H, 6.36; N, 3.43%.

8-Ethyl-7,8-dihydro-4,8-dimethyl-6*H*-indolo[2,1-*a*][2]benzazepine (**1d**). Brown viscous oil; n_D^{25} 1.574; R_f 0.52 (1:3 EtOAc/hexane). IR (Film) ν_{max} 3090, 2970, 1580, 1490, 1450, 1420, 1335, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.90 (3H, t, *J* 9.0 Hz, CH_3), 1.30 (3H, s, CH_3), 1.60 (2H, q, *J* 9.0 Hz, CH_2), 1.80-2.20 (2H, m, *J* 7.5 Hz, CH_2), 2.30 (1H, s, CH), 3.80 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.90-7.90 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 289 (M^+, 15.8), 274 (M^+–CH_3, 72.4), 259 ((M^+–C_2H_5–H, 100), 245 (M^+–CH_3–C_2H_5, 45.2), 244 (88.3), 230 ((M^+–$2CH_3$ –C_2H_5, 14.6), 206 (62.4), 204 (14.2), 191 (14.2), 177 (4.3), 167 (18.2), 151 (7.3), 109 (5.8), 90 (4.5), 77 (5.7), 66 (4.2); Anal. Calcd. for $C_{21}H_{23}N$ (289): C, 87.19; H, 7.95; N, 4.84. Found: C, 87.40; H, 7.62; N, 4.92%.

8-Ethyl-7,8-dihydro-4-methyl-8-phenyl-6*H*-indolo[2,1-*a*][2]benzazepine (**1e**). White crystals, mp 72 °C (benzene); R_f 0.43 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3075, 2965, 1580, 1500, 1430, 1415, 1330, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.90 (3H, t, *J* 9.0 Hz, CH_3), 1.90 (2H, t, *J* 9.0 Hz, CH_2), 2.20-2.50 (2H, m, *J* 7.5 Hz, CH_2), 2.30 (3H, s, CH_3), 3.80 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 7.10-8.20 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 352 (M^++1, 27.4), 351 (M^+, 6.2), 335 (M^+–H–CH_3, 62.8), 322 (M^+–C_2H_5, 100), 307 (34.6), 274 (M^+–Ph, 18.5), 245 (33.8), 230 (42.6), 206 (7.4), 191 (14.2), 177 (12.6), 167 (8.4), 151 (3.7), 109 (7.4), 90 (17.4), 77 (5.3); Anal. Calcd. for $C_{26}H_{25}N$ (351): C, 88.88; H, 7.12; N, 3.98. Found: C, 88.63; H, 7.28; N, 4.15%.

7,8-Dihydro-4,8-dimethyl-8-phenyl-5*H*-indolo[2,1-*a*][2]benzazepine (**1f**). Brownish viscous oil; n_D^{25} 1.542; R_f 0.47 (1:3 EtOAc/hexane); IR (film) ν_{max} 3085, 2984, 1592, 1505, 1470, 1450, 1430, 1330, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.70 (3H, s, CH_3), 2.20-2.50 (2H, m, *J* 7.5 Hz, CH_2), 2.30 (3H, s, CH_3), 3.80 (2H, t, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.90-8.10 (12H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 339 (M^++2, 48.6), 337 (M^+, 7.4), 336 (M^+–H, 100), 322 (M^+–CH_3, 77.4), 307 (M^+–2CH_3, 27.3), 260 (M^+–Ph, 41.7), 245 (M^+–Ph–CH_3, 28.5), 230 (27.2), 206 (11.4), 190 (24.7), 177 (9.6), 166 (7.4), 151 (4.4), 109 (6.4), 90 (12.5), 77 (3.7); Anal. Calcd. for $C_{25}H_{23}N$ (337): C, 89.02; H, 6.82; N, 4.15. Found: C, 89.15; H, 6.92; N, 3.94%.

6,7-Dihydro-4,7,7-trimethylindolo[2,1-*a*]isoquinoline (**2a**). White crystals, mp 140 °C (benzene); R_f 0.36 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3080, 2975, 1610, 1550, 1480, 1435, 1335, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.70 (6H, s, 2CH_3), 2.30 (3H, s, CH_3), 4.10 (2H, s, CH_2), 6.60 (1H, s, CH) and 6.80-8.0 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 262 (M^++1, 57.2), 261 (M^+, 6.8), 246 (M^+–CH_3, 100), 231 (24.7), 216 (M^+–3CH_3, 82.4), 204 (16.7), 192 (25.3), 178 (20.4), 166 (13.5), 151 (4.6), 109 (4.7), 91 (17.4), 77 (3.4), 66 (2.7); Anal. Calcd. for $C_{19}H_{19}N$ (261): C, 87.35; H, 7.27; N, 5.36. Found: C, 87.17; H, 7.42; N, 5.25%.

7-Ethyl-6,7-dihydro-4,7-dimethylindolo[2,1-*a*]isoquinoline (**2b**). Pale yellow crystals, mp 122 °C (benzene); R_f 0.38 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3095, 2979, 1606, 1580, 1480, 1440, 1335, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.90 (6H, t, *J* 9.0 Hz, CH_3), 1.30 (4H, m, *J* 9.0 Hz, CH_2), 1.60 (2H, q, *J* 9.0 Hz, CH_2), 2.30 (3H, s, CH_3), 3.80-4.10 (2H, m, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.80-8.0 (7H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 276 (M^++1, 30.6), 275 (M^+, 4.7), 260 (M^+–CH_3, 92.5), 246 (M^+–C_2H_5, 25.3), 245 (M^+–C_2H_5–H, 100), 231 (M^+–CH_3–C_2H_5, 53.7), 216 (20.4), 202 (26), 188 (13.7), 177 (5.3), 166 (12.5), 151 (2.4), 109 (5.4), 90 (4.7), 77 (4.2), 66 (3.1); Anal. Calcd. for $C_{20}H_{21}N$ (275): C, 87.27; H, 7.63; N, 5.09. Found: C, 87.45; H, 7.53; N, 4.83%.

6,7-Dihydro-4,7-dimethyl-7-phenylindolo[2,1-*a*]isoquinoline (**2c**). White needles, mp 107 °C (benzene); R_f 0.25 (1:3 EtOAc/hexane). IR (KBr) ν_{max} 3090, 2980, 1610, 1575, 1490, 1450, 1342, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.60 (3H, s, CH_3), 2.30 (3H, s, CH_3), 4.10-4.40 (2H, m, *J* 7.5 Hz, CH_2), 6.60 (1H, s, CH) and 6.80-8.20 (12H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 324 (M^++1, 30.4), 323 (M^+, 5.2), 322 (M^+–H, 100), 308 (M^+–CH_3, 62.8), 293 (M^+–2CH_3, 37.5), 246 (M^+–Ph, 69.3), 245 (M^+–Ph–H, 40.2), 231 (15.4), 216 (14.7), 202 (10),

190 (23.5), 177 (8.6), 166 (11.4), 151 (5.3), 109 (5.2), 91 (16.7), 77 (2.5); Anal. Calcd. for $C_{24}H_{21}N$ (323): C, 89.16; H, 6.50; N, 4.33. Found: C, 89.50; H, 6.32; N, 4.15%.

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