New Route of Benzyne Cyclization for Synthesis of 2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indole Derivatives Avoiding Highly Toxic Aryl Hydrazines

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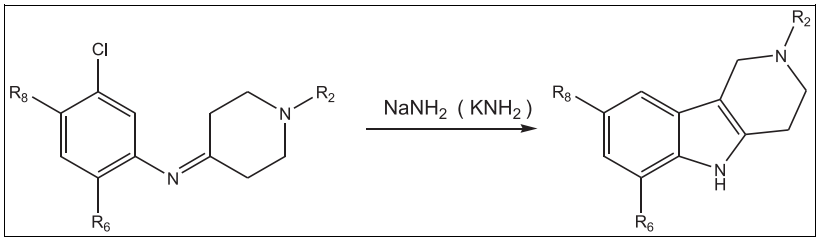

A new route for the regioselective synthesis of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole derivatives was developed based on cyclization of 3-chlorophenylimine-N-alkyl-4-piperidones by "the complex bases" of $NaNH_2$ or KNH_2. The procedure was performed under variable reaction conditions in inert proton-free solvents, such as THF, dioxane, 1,2-dimethoxyethane, toluene, and xylene, at temperatures varying from 20°C to boiling point of the solvent used. Toxic arylhydrazine intermediates occurring in the classical Fischer indole synthesis are avoided.

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INTRODUCTION

Substituted tetrahydropyridoindoles display a broad spectrum of biological and pharmacological activities. Of them, mebhydrolin, 5-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indole, (I, Fig. 1) [1], dimebon, 2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b] indole (II, Fig. 1) [2], and alosetron, 5-methyl-2-[(4-methyl-1H-imidazol-5-yl)methyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (III, Fig. 1) [3] are clinically used as antihistamine agents and serotonin antagonists. Dimebon was clinically tested to treat Alzheimer and Huntington diseases, yet owing to negative side effects, the drug has remained unlicensed for any neurodegenerative diseases.

One of the most elaborated methods to prepare 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b] indoles is Fischer indole synthesis [4] based on the reaction of arylhydrazines and 4-piperidones in acid environment. The disadvantage of this method is the use of arylhydrazines, which are instable, highly toxic, and mutagenic. In the technological process, their use puts great demand on working security and environment protection. The method yields uniform products only for symmetrically substituted arylhydrazines and 4-piperidones. The use of non-symmetric 3-substituted arylhydrazines leads to a non-selective reaction and to the production of regioizomers [5]. In the case of 2-substituted derivatives, transposition and elimination of functional groups occurs on the aromatic skeleton in position 2, relative to hydrazine function [6]. These facts often complicate product isolation and decrease the yield.

The Graebe-Ullmann method [7] retains the same problems of regioselectivity and complexity of the Fischer procedure. Its principle is thermic, photolytic or microwave breakdown of 1-aryl-1H-1,2,3-triazolo(4,5-c)pyridines [8], or of 1-pyridyl-1H-1,2,3-benzotriazoles [9].

Thermic cyclization of 3-(2-azidophenyl)pyridines [10] or of 3-(2-nitrosophenyl)pyridines [11] represents an analogous non-selective procedure. The same is true for photochemical cyclizations of 4-aniline-pyridines [12] and N-arylenamine-4-amine-piperidones [13].

Other methods employ cyclization of 2-(2-indolyl)ethyl-aza-cumulenes [14], 2-(2-indolyl)ethylaldimines [15] or of acylated 2-(2-indolyl)ethylamines [16]. Because of a high number of reaction steps, they are just of laboratory relevance.

Similar drawbacks are characteristic for synthetic procedures based on thermic breakdown of 2-vinyl-3-azidomethylindoles [17], derivatization of 1-metoxyindol-2-karbaldehyde [18,19], Diels-Alder's reactions of 3-formimidoyl- and 2-ethoxyindoles [20,21], or for retro-Mannich reaction of tetrahydropyrimido (1,6-a)indoles [22].

Disadvantages of the aforementioned procedures employed for the synthesis of tetrahydropyridoindoles are partially eliminated by Heck's reaction of 2-iodine aniline with N-ethoxycarbonyl-4-piperidones under catalysis of $Pd(OAc)_2$ in dimethylformamide. However, this approach was used only in a particular case [23] and moreover, isolation of the product required chromatographic separation.

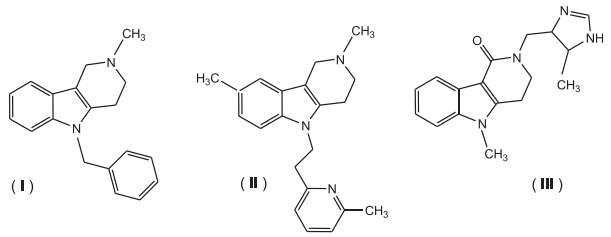
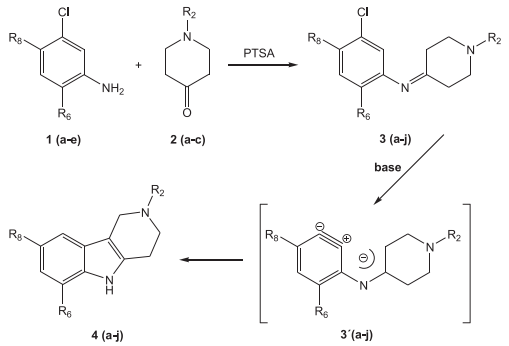


Figure 1. Chemical structure of mebhydrolin (I), dimebon (II) and alosetron (III).

The method of aryne cyclization plays an important role in the synthesis of indoles and other heterocyclic compounds. Intramolecular C-nucleophil aryne coupling gives rise to condensed cyclic and heterocyclic systems. This synthetic strategy, also called benzyne cyclization, has a broad use in the preparation of four-member, five-member, and six-member rings or higher ones. The most frequently used methods of dehydroarene preparation comprise the reaction of arylhalogenides with strong bases [24,25]. The bases most frequently used include amides of alkali metals in the liquid ammonia or inert aprotic solvents [26,27] . Mixtures of amides of alkali metals with appropriate alcoholates of alkali metals (e.g., t-BuONa), which react together and give rise to so-called complex bases in inert aprotic solvents, mostly in ethers, are also used [28]. Organolithium compounds, such as lithium diisopropylamide [29] or t-butyllithium (t-BuLi) [30,31] can be used as alternative basis for aryne generation.

Scheme 1. Synthetic route of substituted 2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indole derivatives.



The cyclization 3-chlorophenylimine-N-alkyl-4-piperidones, described in this paper, represents a highly efficient method of the regioselective synthesis of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indoles, with minimum damage to environment because the procedure avoids toxic arylhydrazine intermediates.

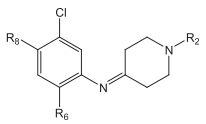
RESULTS AND DISCUSSION

In the present paper, we describe the synthesis of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole derivatives based on cyclization of 3-chlorophenylimine-N-alkyl-4-piperidones with $NaNH_2$ or KNH_2, under variable reaction conditions in inert proton-free solvents, such as THF, dioxane, 1,2-dimethoxyethane, toluene, or xylene (Scheme 1). The starting imines (Schiff bases) **3a–j** were prepared according to the literature with good yields by interaction of appropriately substituted 3-chloroanilines (**1a–e**) and N-alkyl-piperidones (**2a–c**) under catalysis of p-toluenesulfonic acid. The solvents used, yields, and final purities of the precursor imines **3a–j** are summarized in Table 1.

Generally, on synthesizing indole derivatives from imines, complex bases are used, e.g., prepared by interaction of sodium amide with sodium t-butanolate. Addition of alcoholate helps dissolution of sodium amide in aprotic

Table 1

Synthesis of the imine precursors **3a–j**.



Comp	R^2	R^6	R^8	Solvent	Purity (%) (GC–MS)	Boiling point	Yield (%)
3a	CH_3	H	H	Cyclohexane	88.3	125–130°C/1 mmHg	69.8
3b	CH_3	H	CH_3	Cyclohexane	94.6	133–136°C/1 mmHg	74.8
3c	CH_3	H	CH_3O	Benzene	87.5	148–153°C/1 mmHg	72.5
3d	CH_3	CH_3	H	Cyclohexane	86.4	132–136°C/1 mmHg	65.3
3e	CH_3	CH_3O	H	Toluene	50.3 (crude)	—	—
3f	CH_2Ph	H	H	Toluene	56.4 (crude)	—	—
3g	CH_2Ph	H	CH_3	Toluene	51.4 (crude)	—	—
3h	$(CH_2)_2Ph$	H	H	Toluene	35.2 (crude)	—	—
3i	$(CH_2)_2Ph$	H	CH_3	Toluene	33.4 (crude)	—	—
3j	$(CH_2)_2Ph$	H	CH_3O	Toluene	38.2 (crude)	—	—

solvents (e.g., THF, toluene) so that the reaction is carried on in a homogenous medium. Relative to the precursor imine, five equivalents of $NaNH_2$ (KNH_2) are optimally used with two equivalents of t-BuONa (t-BuOK). According to our results, the reaction can be performed with profoundly decreased molar ratios of the basic components relative to the imine precursor, yet with still reasonably high yields, when using crown ether (4b-16, 18-crown6), polyethyleneglycol (4b-17, PEG-500; 4b-18, PEG-6000), or the catalyst of phase transfer tetrabutyl ammonium chloride (4b-19, TBACH), as shown in Table 2. Prolongation of the reaction time from 24 to 48 h, on using THF, dioxane, or dimethoxyethane solvents, may significantly increase the yield even with decreased content of the complex bases. Similar yields were obtained when organolithium compounds (4a-2, 4b-5, 4b-6, t-BuLi; 4b-7, lithium di-isopropyl amide) were used to cyclize the imine. The reaction performed with $NaNH_2$ alone in THF (4b-22, 4b-23) gave significantly lower yields in comparison with reactions performed with $NaNH_2$ in the presence of the aforementioned catalysts (Table 2). The synthesis employing a high excess of the Grignards reagent (4b-8) failed completely.

To conclude, a new route for the regioselective synthesis of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole derivatives was developed on the basis of cyclization of 3-chlorophenylimine-N-alkyl-4-piperidones by "the complex bases" of $NaNH_2$ or KNH_2. The procedure was performed under variable reaction conditions avoiding toxic arylhydrazines as intermediates of the classical Fischer indole synthesis and as such represents an example of contemporary chemistry friendly to the environment.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on Bruker Avance DPX 300 spectrometer (Bruker Biospin SA, Wissenbourg, France) operating at 300.13 MHz for ^1H and 75.46 MHz for ^{13}C. ^1H-NMR and ^{13}C-NMR spectra were acquired using internal acetone (^1H $\delta = 2.225$; ^{13}C $\delta = 31.07$) as a reference standard in $CDCl_3$ or D_2O used as solvents. To assign the signals, the COSY, HSQC, TOCSY, NOESY, and DEPT techniques were used. Elemental analyses were performed on EA 1108 Carlo Erba. Melting points were determined on a Kofler melting point apparatus (Franz Küstner, Dresden, Germany) with digital thermometer (DT012C) and are uncorrected. Mass spectra were recorded on mass detector HP 5970B MSD (Hewlett-Packard, Palo Alto, CA, USA) at 70 eV ionization. The purity of the intermediate products was determined by GC–MS on HP 5890/5970B GC-MS System (Hewlett-Packard, Palo Alto, CA, USA) using the column HP-5 (12 m × 0.22 mm × 0.33 μm). The precursor 3-chloroanilines (3-chloroaniline **1a**, 3-chloro-4-methylaniline **1b**, 3-chloro-4-methoxylaniline **1c**, 3-chloro-6-methylaniline **1d**, and 3-chloro-6-methoxylaniline **1e**) and N-alkyl-4-piperidones (N-methyl-4-piperidone **2a**, N-benzyl-4-piperidone **2b**, and N-fenethyl-4-piperidone **2c**) were purchased from Sigma-Aldrich. Other chemicals were purchased from local commercial sources. All solvents and reactants were purified before use according to standard procedures [32].

Precursor imines (3a–j): general procedure. The stirred mixture of appropriately substituted 3-chloroanilines (**1a–e**, 1.2 mol) and N-alkyl-4-piperidones (**2a–c**, 1 mol) in a corresponding solvent (500 mL) was refluxed under catalysis by p-toluenesulfonic acid monohydrate (PTSA. H_2O, 2g). Water generated during the reaction was continuously removed by azeotropic distillation. After completion of the reaction, the solvent was evaporated under reduced pressure, and the crude reaction product (**3a–j**) was further purified by vacuum distillation or used for the next reaction step without purification. Reaction conditions, yields, and purity of the products **3a–j** are shown in Table 1.

Substituted 2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indoles (4a–j).

Procedure 1. Solid sodium t-butanolate was added to the stirred suspension of sodium amide $NaNH_2$ in 15 mL dry solvent, and the reaction mixture was heated to 55–60°C for 2 h, followed by cooling to 0–5°C under argon atmosphere. A solution of an appropriately substituted imine (**3**, 10 mmol) in 10 mL of dry solvent was added dropwise, and then the reaction mixture was heated again for the reaction time indicated. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product **4a–j** crystallized from appropriate solvent. Molar ratios of the bases employed, solvent used, reaction temperature and time, yield, purity, solvent used for crystallization, and melting points are summarized in Table 2.

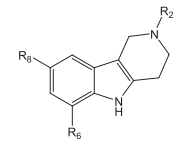
Procedure 2. The solution of 3-chlorophenylimine-N-methyl-4-piperidone (**3a**, 10 mmol) or 3-chloro-4-methylphenylimine-N-methyl-4-piperidone (**3b**, 10 mmol) in 10 mL of dry THF was added dropwise to the stirred solution prepared by mixing 20 mL t-butyllithium in pentane (30 mmol) and 20 mL of dry THF at −80°C, and then the reaction mixture was heated under argon atmosphere to 20–25°C for the indicated reaction time. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4a**,**b**) crystallized from the appropriate solvent. Molar ratios of the bases employed, solvent used, reaction temperature and time, yield, purity, solvent used for crystallization, and melting points are summarized in Table 2.

Procedure 3. The solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone (**3b**, 10 mmol) in 10 mL of dry THF was added dropwise to the stirred solution prepared by mixing 15 mL of lithium diisopropylamide in THF (30 mmol) and 20 mL of dry THF at −80°C, and then the reaction mixture was heated to 20–25°C for 24 h under argon atmosphere. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

Procedure 4. The solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone (**3b**, 10 mmol) in 10 mL of dry THF was

Table 2

Synthesis of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indoles 4a-j.



Comp (batch)	R^2	R^6	R^8	Synthetic procedure	Base (equivalent relative to **3a–j**)	T (°C)	Solvent/reaction time (hour)	Yield (purity) (%)	Melting point (°C) (Crystallized from)
4a (1)	CH_3	H	H	1	$NaNH_2$/t-BuONa (5:2)	60	THF/24	88.2 (99.2)	168–170 (B)
4a (2)	CH_3	H	H	2	t-BuLi (3)	20–25	THF/24	68.6 (99.1)	168–170 (B)
4b (1)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	92.1 (99.8)	153–155 (T)
4b (2)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (5:2)	60	Toluén/24	78.3 (99.1)	153–155 (T)
4b (3)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (4:2)	60	Toluén/24	52.6 (98.7)	153–155 (T)
4b (4)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (4:2)	60	THF/24	76.2 (99.3)	153–155 (T)
4b (5)	CH_3	H	CH_3	2	t-BuLi (3)	−80–+25	THF/48	66.2 (98.7)	153–155 (T)
4b (6)	CH_3	H	CH_3	2	t-BuLi (4)	−80-+25	THF/48	74.3 (98.6)	153–155 (T)
4b (7)	CH_3	H	CH_3	3	Lithium diisopropylamide (3)	−80–+25	THF/24	75.9 (98.3)	153–155 (T)
4b (8)	CH_3	H	CH_3	4	t-BuMgCl (8)	60	THF/48	0.5[a]	—
4b (9)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (3.5:1)	90	Toluén/48	52.8 (99.4)	153–155 (T)
4b (10)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (2.6:0.5)	110	Toluén/48	53.6 (99.2)	153–155 (T)
4b (11)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (2.6:0.5)	110	Xylén/48	53.6 (99.3)	153–155 (T)
4b (12)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (2.1:0.05)	60	THF/48	72.4 (98.7)	153–155 (T)
4b (13)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (3:0.05)	60	THF/48	88.2 (99.8)	153–155 (T)
4b (14)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (3:0.05)	60	Dioxán/48	82.4 (99.2)	153–155 (T)
4b (15)	CH_3	H	CH_3	5	KNH_2:t-BuOK (5:2)	60	THF/24	93.6 (99.8)	153–155 (T)
4b (16)	CH_3	H	CH_3	6	KNH_2:18-crown6 (3:0.05)	60	THF/48	77.8 (98.9)	153–155 (T)
4b (17)	CH_3	H	CH_3	7	$NaNH_2$:PEG500 (3:0.05)	60	THF/48	68.9 (98.7)	153–155 (T)
4b (18)	CH_3	H	CH_3	7	$NaNH_2$:PEG6000 (3:0.05)	60	THF/48	69.7 (99.1)	153–155 (T)
4b (19)	CH_3	H	CH_3	8	$NaNH_2$:TBACH[b] (3:0.05)	60	THF/48	67.4 (99.3)	153–155 (T)
4b (20)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (3:0.05)	60	THF/48	88.6 (99.7)	153–155 (T)
4b (21)	CH_3	H	CH_3	9	$NaNH_2$:t-BuONa (3:0.15)	20-25	1.2-DME[c]/48	86.5 (98.6)	153–155 (T)
4b (22)	CH_3	H	CH_3	10	$NaNH_2$ (3)	60	THF/48	41.4 (98.1)	153–155 (T)
4b (23)	CH_3	H	CH_3	10	$NaNH_2$ (5)	60	THF/48	48.9 (97.8)	153–155 (T)
4b (24)	CH_3	H	CH_3	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	68.5 (98.7)	153–155 (T)
4c (1)	CH_3	H	CH_3O	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	85.7 (99.1)	170–171 (M)
4c (2)	CH_3	H	CH_3O	1	$NaNH_2$:t-BuONa (3:0.05)	60	THF/48	76.7 (98.8)	170–171 (M)
4d (1)	CH_3	CH_3	H	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	83.5 (98.4)	127–129 (E)
4d (2)	CH_3	CH_3	H	1	$NaNH_2$:t-BuONa (3:0.05)	60	THF/48	74.9 (98.8)	127–129 (E)
4e (1)	CH_3	CH_3O	H	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	40.6[d] (97.8)	170–171 (M)
4f (1)	$PhCH_2$	H	H	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	67.8 (98.3)	154–155 (E)
4g (1)	$PhCH_2$	H	CH_3	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	74.3 (97.4)	178–179 (E)
4h (1)	$Ph(CH_2)_2$	H	H	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	62.3 (97.3)	161–162 (E)
4i (1)	$Ph(CH_2)_2$	H	CH_3	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	59.8 (97.5)	155–157 (T)
4j (1)	$Ph(CH_2)_2$	H	CH_3O	1	$NaNH_2$:t-BuONa (5:2)	60	THF/24	65.7 (96.8)	133–135 (E)

[a]The yield was determined by GC–MS, [b]Tetrabutylammonium chloride, [c]1,2-DME (1,2-dimethoxyethane), [d]Reaction mixture was purified by chromatography. (B), benzene; (E), ethanol; (M), methanol; (T), toluene.

added dropwise to the stirred solution prepared by mixing 15 mL of t-BuMgCl in THF (80 mmol) and 20 mL of dry THF at −80°C, and then the reaction mixture was heated to 60°C for 48 h under argon atmosphere. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**). The yield, purity, and melting point are summarized in Table 2.

Procedure 5. Potassium t-butanolate (20 mmol) was added to the stirred suspension of potassium amide KNH_2 (50 mmol) in 30 mL of dry THF, and the reaction mixture was heated to 55–60°C for 2 h, followed by cooling to around 20°C under argon atmosphere. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (10 mmol) in 10 mL dry THF was added dropwise, and then the reaction mixture was heated again to 55–60°C for 24 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene The yield, purity, and melting point are summarized in Table 2.

Procedure 6. The 18-Crown-6 (0.5 mmol) was added to the stirred suspension of potassium amide (KNH_2, 30 mmol) in 15 mL dry THF. The reaction mixture was heated to 55–60°C for 0.5 h, followed by cooling to around 20°C under argon atmosphere. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (10 mmol) in 10 mL dry THF was added dropwise, and then the reaction mixture was heated again to 55–60°C for 48 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

Procedure 7. PEG 500 or PEG 6000 (0.5 mmol) was added to the stirred suspension of sodium amide $NaNH_2$ (30 mmol) in 15 mL dry THF, and the reaction mixture was heated to 55–60° C for 0.5 h, followed by cooling to around 20°C under argon atmosphere. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (10 mmol) in 10 mL dry THF was added dropwise, and then the reaction mixture was heated again to 55–60°C for 48 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

Procedure 8. Tetrabutylammonium chloride (0.5 mmol) was added to the stirred suspension of sodium amide $NaNH_2$ (30 mmol) in 15 mL dry THF, and the reaction mixture was heated to 55–60°C for 0.5 h, followed by cooling to around 20°C under argon atmosphere. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (10 mmol) in 10 mL dry THF was added dropwise, and then the reaction mixture was heated again to 55–60°C for 48 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

Procedure 9. Sodium t-butanolate (6.33 mmol) was added to the stirred suspension of sodium amide $NaNH_2$ (126.6 mmol) in 100 mL dry 1,2-dimethoxyethane, and the reaction mixture was heated to 55–60°C for 2 h, followed by cooling to around 20°C under argon atmosphere. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (42.2 mmol) in 40 mL dry 1,2-dimethoxyethane was added dropwise, and then the reaction mixture was heated again to 55–60°C for 48 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product (**4b**) crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

Procedure 10. A solution of 3-chloro-4-methylphenylimine-N-methyl-4-piperidone **3b** (10 mmol) in 10 mL dry THF was added dropwise to the stirred suspension of sodium amide $NaNH_2$ (30 or 50 mmol) in 15 mL dry solvent, and then the reaction mixture was heated to 55–60°C for 48 h. The solvent was evaporated under reduced pressure to dryness. The crude product was dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated in vacuum. The residue was dissolved in the mixture of toluene: triethylamine (10:1), filtered through a short column of silica gel (6 g, 40–63 μm), and evaporated again to dryness in vacuum to afford crude product **4b** crystallized from toluene. The yield, purity, and melting point are summarized in Table 2.

2-Methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4a). White solid; mp 168–170°C (Benzene); ^{1}H-NMR ($CDCl_3$): δ 2.54 (s, 3H, N–CH_3), 2.54 (t, 2H, H-4), 2.73 (t, 2H, H-3), 3.66 (s, 2H, H-1), 7.05–7.37 (m, 4H, H–Ar), 8.74 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.40 (C-4), 45.70 (N–CH_3) 51.70 (C-1), 52.40 (C-3), 108.15 (C-9b), 110.60 (C-6), 117.30 (C-7), 119.00 (C-8), 120.90 (C-9), 125.93 (C-4a), 131.91 (C-9a), 136.15 (C-5a). MS *m/z* (%): 186 (M^+, 24), 143 (100), 115 (11), 93 (4), 77 (6). *Anal.* Calcd for $C_{12}H_{14}N_2$ (186.25): C, 77.38; H, 7.57; N, 15.04. Found: C, 77.13; H, 7.73; N, 15.14.

2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4b). White solid; mp 153–155°C (Toluene); ^{1}H-NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3-8), 2.54 (s, 3H, N–CH_3), 2.68 (t, 2H, H-3), 2.76 (t, 2H, H-4), 3.63 (s, 2H, H-1), 6.90–7.17 (m, 3H, H–Ar), 8.23 (bs, NH); ^{13}C-NMR ($CDCl_3$): 21.55 (CH_3-8), 23.76 (C-4), 45.87 (N–CH_3), 51.84 (C-3), 52.56 (C-1), 108.10 (C-9b), 110.34 (C-6), 117.34 (C-9), 122.53 (C-7), 126.37 (C-4a), 128.33 (C-9a), 132.05 (C-5a), 134.53 (C-8). MS *m/z* (%): 200 (M^+, 21), 157 (100), 128 (4), 115 (4), 99 (5). *Anal.* Calcd for $C_{13}H_{16}N_2$ (200.28): C, 77.96; H, 8.05; N, 13.98. Found: C, 77.77; H, 8.28; N, 13.87.

2-Methyl-8-methoxy-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4c). White solid; mp 170–171°C (Methanol); ^{1}H-NMR ($CDCl_3$): δ 2.80 (t, 4H, H-3, H-4), 3.58 (s, 3H, N-CH_3), 3.66 (s, 2H, H-1), 3.85 (s, 3H, CH_3O-8) 6.75–7.10 (m, 3H, H–Ar),

8.05 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.85 (C-4), 45.80 (N–CH_3), 51.75 (C-1), 52.44 (C-3), 55.90 (CH_3O-8), 100.03 (C-9), 108.54 (C-9b), 110.60 (C-7), 111.17 (C-6), 126.42 (C-4a), 131.19 (C-9a), 132.72 (C-5a), 153.85 (C-8). MS *m/z* (%): 216 (M^+, 23), 187 (3), 173 (100), 158 (55), 142 (4), 130 (8), 103 (5), 77 (6). *Anal.* Calcd for $C_{13}H_{16}N_2O$ (216.28): C, 72.19; H, 7.45; N, 12.95. Found: C, 72.34; H, 7.21; N, 13.22.

2,6-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4d). White solid; mp 127–129°C (Ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3-6), 2.58 (s, 3H, N–CH_3), 2.85 (t, 2H, H-4), 2.89 (t, 2H, H-3), 3.71 (s, 2H, H-1), 6.96–7.28 (m, 3H, H–Ar), 7.96 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.67 (C-4), 45.65 (N–CH_3), 51.87 (C-1), 52.42 (C-3), 55.32 (CH_3O-6), 101.67 (C-7), 108.91 (C-9b), 110.59 (C-9), 119.54 (C-8), 126.34 (C-5a), 127.32 (C-4a), 131.21 (C-9a), 145.78 (C-6). MS *m/z* (%): 200 (M^+, 22), 157 (100), 128 (4), 115 (6), 77 (4), 63 (3). *Anal*. Calcd for $C_{13}H_{16}N_2$ (200.28): C, 77.96; H, 8.05; N, 13.98. Found: C, 77.78; H, 8.41, N, 13.81.

2-Methyl-6-methoxy-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4e). White solid; mp 170–171°C (Methanol); ^{1}H-NMR ($CDCl_3$): δ 2.58 (s, 3H, N-CH_3), 2.86 (t, 4H, H-3, H-4), 3.70 (s, 2H, H-1), 3.95 (s, 3H, CH_3O-6), 6.63–7.03 (m, 3H, H–Ar), 8.20 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.67 (C-4), 45.65 (N–CH_3), 51.87 (C-1), 52.42 (C-3), 55.32 (CH_3O-6), 101.67 (C-7), 108.91 (C-9b), 110.59 (C-9), 119.54 (C-8), 126.34 (C-5a), 127.32 (C-4a), 131.21 (C-9a), 145.78 (C-6). MS *m/z* (%): 216 (M^+, 30), 173 (100), 158 (38), 130 (7), 108 (8), 77 (5), 63 (3). *Anal*. Calcd for $C_{13}H_{16}N_2O$ (216.28): C, 72.19; H, 7.45; N, 12.95. Found: C, 72.42; H, 7.18; N, 13.05.

2-Benzyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4f). White solid; mp 154–155°C (Ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.70 (t, 2H, H-3), 2.84 (t, 2H, H-4), 3.71 (s, 2H, H-1), 3.78 (s, 2H, CH_2–C_6H_5), 7.00–7.20 (m, 4H, H–Ar), 7.20–7.55 (m, 5H, H–Ph), 7.89 (bs, NH). ^{13}C-NMR ($CDCl_3$): 23.73 (C-4), 49.86 (C-1), 50.21 (C-3), 62.47 (CH_2–Ph), 108.75 (C-9b), 110.70 (C-6), 117.61 (C-9), 119.29 (C-8), 121.19 (C-7), 126.22 (C-4a), 132.25 (C-9a), 136.12 (C-5a), 127.23, 128.50, 129.26, 138.63, 138.63 (C–Ph). MS *m/z* (%): 262 (M^+, 24), 143 (100), 115 (7), 91 (22), 65 (6). *Anal*. Calcd for $C_{18}H_{18}N_2$ (262.35): C, 82.40; H, 6.91; N, 10.67. Found: C, 82.64; H, 7.11; N, 10.25.

2-Benzyl-8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4g). White solid; mp 178–179°C (Ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3-8), 2.68 (t, 2H, H-3), 2.83 (t, 2H, H-4), 3.67 (s, 2H, H-1), 3.77 (s, 2H, CH_2–C_6H_5), 6.89–7.13 (m, 3H, H–Ar), 7.25–7.45 (m, 5H, H–Ph), 7.75 (bs, NH); ^{13}C-NMR ($CDCl_3$): 21.43 (CH_3-8), 23.64 (C-4), 49.74 (C-1), 50.20 (C-3), 62.37 (CH_2–Ph), 108.60 (C-9b), 110.22 (C-6), 117.33 (C-9), 122.49 (C-7), 126.37 (C-4a), 128.31 (C-9a), 132.23 (C-5a), 134.32 (C-8), 128.31, 129.15, 138.62 (C–Ph). MS *m/z* (%): 276 (M^+, 18), 183 (4), 157 (100), 128 (3), 91 (20), 65 (5). *Anal*. Calcd for $C_{19}H_{20}N_2$ (276.38): C, 82.57; H, 7.29; N, 10.13. Found: C, 82.70, H, 7.09; N, 10.21.

2-(2-Fenethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4h). White solid; mp 161–162°C (Ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.83 (t, 2H, H-4), 2.94 (m, 2H, CH_2–Ph), 2.97 (m, 2H, N–CH_2), 2.97 (t, 2H, H-3), 3.85 (s, 2H, H-1), 7.11–7.28 (m, 4H, H–Ar), 7.11–7.35 (m, 5H, H–Ph), 7.88 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.30 (C-4), 34.33 (N-CH_2), 49.53 (C-1), 50.80 (C-3), 60.34 (CH_2–Ph), 108.58 (C-9b), 110.60 (C-6), 117.30 (C-7), 119.00 (C-8), 120.41 (C-9), 126.16 (C-4a), 132.00 (C-9a), 136.15 (C-5a), 126.30, 128.51, 128.58, 140.35 (C–Ph). MS *m/z* (%): 276 (M^+, 11), 185 (82), 156 (100), 143 (30), 115 (8), 91 (9), 77 (8). *Anal*. Calcd for $C_{19}H_{20}N_2$ (276.38): C, 82.57; H, 7.29; N, 10.13. Found: C, 82.42; H, 7.55; N, 10.01.

2-(2-Fenethyl)-8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4i). White solid; mp 155–157°C (Toluene); ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3-8), 2.78 (t, 2H, H-4), 2.90 (m, 2H, H-3), 2.91 (m, 2H, N–CH_2), 2.93 (m, 2H, CH_2–C_6H_5), 3.78 (s, 2H, H-1), 6.92–7.20 (m, 3H, H–Ar), 7.15–7.40 (m, 5H, H–Ph), 7.83 (bs, NH); ^{13}C-NMR ($CDCl_3$): 21.45 (CH_3-8), 23.73 (C-4), 34.27 (N–CH_2), 49.46 (C-1), 50.78 (C-3), 60.00 (CH_2–Ph), 108.03 (C-9b), 110.20 (C-6), 117.30 (C-9), 122.55 (C-7), 126.39 (C-4a), 128.39 (C-9a), 132.13 (C-5a), 134.36 (C-8), 128.39, 128.71, 140.34 (C–Ph). MS *m/z* (%): 290 (M^+, 44), 199 (80), 170 (100), 157 (35), 91 (7), 65 (4). *Anal*. Calcd for $C_{20}H_{22}N_2$ (290.41): C, 82.71; H, 7.63; N, 9.64. Found: C, 82.35; H, 7.94; N, 9.70.

2-(2-Fenethyl)-8-methoxy-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4j). White solid; mp 133–135°C (Ethanol); ^{1}H-NMR ($CDCl_3$): δ 2.61 (t, 2H, H-4), 2.89 (t, 2H, H-3), 2.95 (m, 2H, CH_2-C_6H_5), 2.98 (m, 2H, N–CH_2), 3.83 (s, 2H, H-1), 3.88 (s, 3H, CH_3O-8), 6.77–7.01 (m, 3H, H–Ar), 7.15–7.38 (m, 5H, H–Ph), 8.42 (bs, NH); ^{13}C-NMR ($CDCl_3$): 23.43 (C-4), 34.00 (N-CH_2), 49.33 (C-1), 50.85 (C-3), 55.79 (CH_3O-8), 60.00 (CH_2–Ph), 99.75 (C-9), 107.77 (C-9b), 110.43 (C-7), 111.23 (C-6), 126.31 (C-4a), 131.19 (C-5a), 133.00 (C-9a), 132.65 (C-8), 126.00, 128.33, 128.60, 140.11 (C–Ph). MS *m/z* (%): 306 (M^+, 15), 215 (70), 186 (100), 173 (26), 158 (25), 108 (7), 77 (9). *Anal*. Calcd for $C_{20}H_{22}N_2O$ (306.40): C, 78.40; H, 7.23; N, 9.14. Found: C, 78.35; H, 7.34; N, 9.07.

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