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Synthesis of 1-phenyl- and 1-pyridyl-3-pyridoazepines by reductive cyclization of diarylacetonitriles

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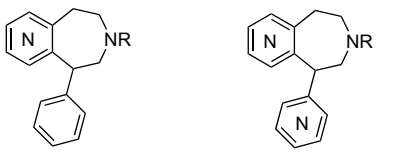
ABSTRACT

Several pyrido[2,3-*d*]azepines and pyrido[3,4-*d*]azepines, novel aza analogs of the pharmacologically relevant 1-aryl-3-benzazepines, were synthesized by assembling the azepine ring by reductive cyclization of (2-methoxyvinyl)pyridinyl(aryl)acetonitrile derivatives, which were easily derived from contiguously substituted bromo(2-methoxyvinyl)pyridines and the corresponding arylacetonitriles.

1. Introduction

The neurotransmitter dopamine (DA) is involved in various physiological and pathological processes, including brain functions such as motion, emotion, and cognition. DA antagonists are used for treating schizophrenia, mania, delirium, and Huntington's disease, and DA agonists for treating Parkinson's disease and neuroendocrine disorders.[1] However, the limitations of current DA agonists and antagonists maintain interest in the search for novel analogs, especially with regard to the improvement of selectivity for particular DA receptor subtypes. The prototype D_1-selective antagonist, SCH 23390,[2] is a 1-aryl-3-benzazepine, a family that, if conformationally restricted derivatives are counted, now includes the agonists SKF 38393,[3] SKF 82526 (fenoldopam),[4] and SKF 82958,[5] and the antagonist SCH 39166.[6] In all these compounds the 1-aryl moiety is essential for affinity and selectivity for D_1-like receptors.[7]

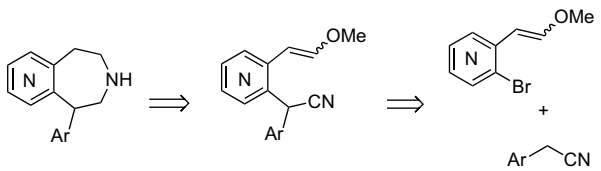


1-phenyl-3-pyridoazepine 1-pyridyl-3-pyridoazepine

Figure 1. Aza analogs of 1-phenyl-3-benzazepines.

In this work we investigated the synthesis of two new series of analogs in which the fused benzene ring is replaced by a fused pyridine, namely the 1-phenyl-3-pyridoazepines and 1-pyridyl-3-pyridoazepines (Fig. 1). Although 5*H*-pyrido[2,3-*d*]azepines[8] and 5*H*-pyrido[3,4-*d*]azepines[9] have appeared in the literature, as have 1-pyridyl-3-benzazepines,[10] compounds incorporating the 1-aryl-3-pyridoazepine scaffold have not previously been reported.

In accordance with the retrosynthetic analysis shown in Scheme 1, we planned to prepare the target 1-aryl-3-pyridoazepines by coupling bromo(2-methoxyvinyl)pyridines and arylacetonitriles, followed by ring closure. Since pyridine is π-deficient, and the resonance effect of the N atom results in the α and γ positions bearing a partial positive charge that makes them prone to nucleophilic attack, we envisaged that bromopyridines **3a** and **3c** could be linked directly to the arylacetonitrile by an S_NAr reaction (addition–elimination) following base-induced formation of the corresponding anion (Scheme 2).[11] In the case of bromopyridine **3b**, it was hoped that palladium-catalyzed arylation of phenylacetonitrile[12] would achieve the coupling. For ring closing, a variety of methods would be tried.



Scheme 1. Retrosynthetic analysis of pyridoazepines.

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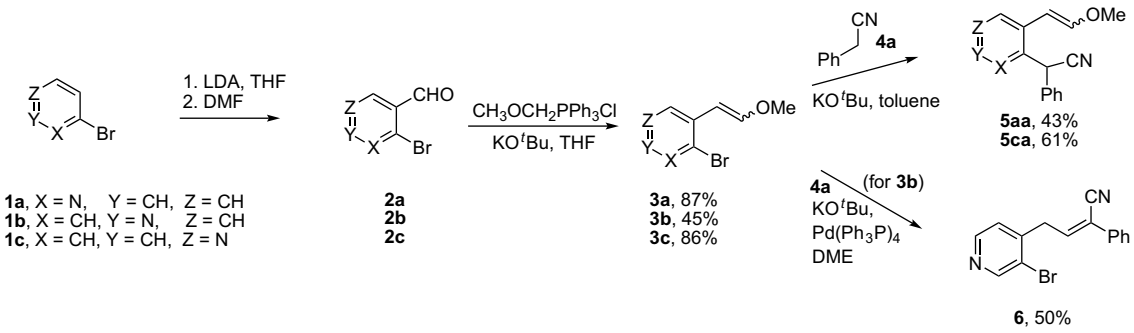


Scheme 2. Synthesis of diarylacetonitriles **5aa** and **5ca**.

2. Results and discussion

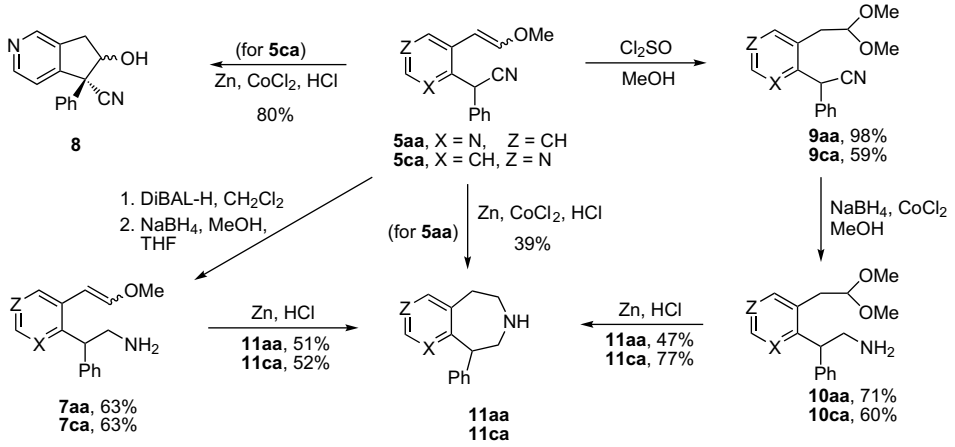
2.1. Synthesis of 1-phenyl-3-pyridoazepines

To prepare bromo(2-methoxyvinyl)pyridines **3a–c** from bromopyridines **1a–c**, bromopyridine carbaldehydes **2a–c** were first prepared by lithiation of **1a–c** followed by formylation with DMF.[13] The homologations of the aldehydes were then achieved by Wittig reactions with methoxymethyl triphenylphosphonium chloride and KO^{t}Bu. This afforded good yields of **3a** and **3c** as mixtures of *E* and *Z* isomers (Scheme 2), but only about half as much of the 3-bromo derivative **3b** (although in this case the *E* and *Z* isomers were separated; the combined yield of the geometrically pure vinyl ethers was 45%). Nitriles **5aa** and **5ca** were obtained as planned, though in moderate yield, by S_NAr displacements on bromopyridines **3a** and **3c** with phenylacetonitrile (**4a**) by heating in toluene at 80 °C in the presence of KO^{t}Bu. However, palladium-catalyzed coupling of **3b** to phenylacetonitrile did not afford their isomer **5ba**, but compound **6**, probably as the result of a competitive conjugated nucleophilic attack by the phenylacetonitrile anion on the methoxy-substituted vinylic carbon, followed by elimination of methanol and isomerization of the double bond to the more substituted alkene.

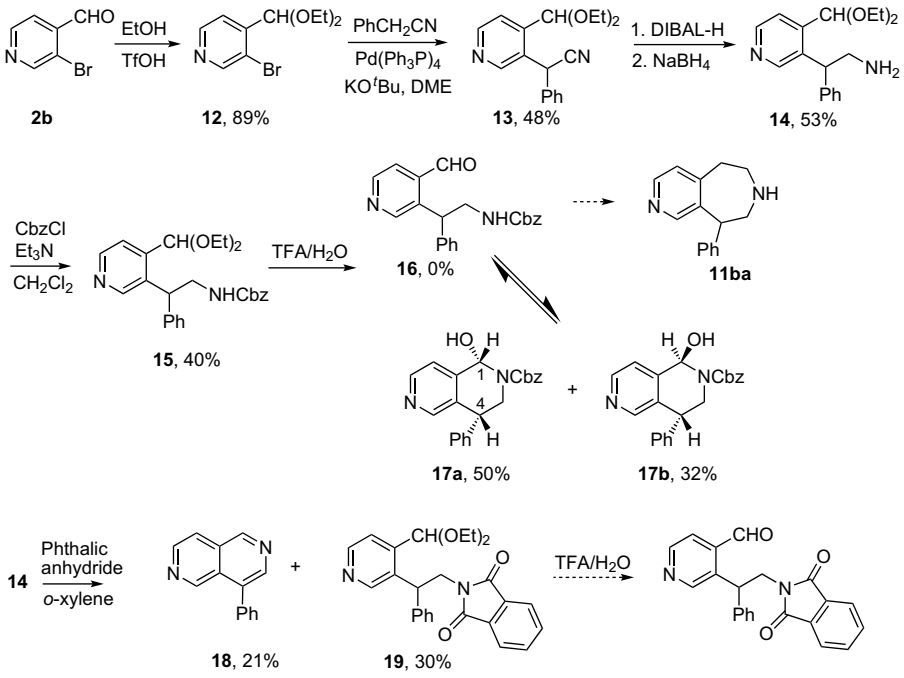
For the cyclization of nitriles **5aa** and **5ca** we first considered their reduction to the corresponding amines **7**, followed by in situ acid catalyzed intramolecular condensation with the aldehyde obtained by hydrolysis of the vinyl ether and further reduction of the resulting imine. This kind of one-pot reductive cyclization has been used in the synthesis of 3-benzazepines from nitro acetals.[10] In our case, reduction of the nitrile group of **5aa** by treatment with a large excess of Zn and $CoCl_2$ in 6 M HCl[14] gave direct access to 9-phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine (**11aa**) in 39% isolated yield (Scheme 3). By contrast, under the same conditions the isomeric nitrile **5ca** unexpectedly afforded cyclopentane **8** as the major product, no doubt due to aldehyde formation followed by intramolecular nucleophilic attack by the α-carbon of the nitrile. This undesired behavior probably takes place through an α-chloroenamine, which is formed by initial protonation of the nitrile and further addition of HCl to form an intermediate imidoyl chloride,[15] a process that seems not occur in the case of **5aa** because the protonation of the nitrile might be inhibited by electrostatic repulsion from the nearby protonated pyridine nitrogen.[16]

To prevent undesired formation of **8**, a two-step procedure was employed in which the aminoethyl derivatives **7** were isolated before their reductive cyclization. Reduction of nitriles **5aa** and **5ca** with LAH/$AlCl_3$ in diethylether gave only poor yields, but yields of more than 60% were obtained by sequential treatment with DIBAL-H and $NaBH_4$.[17] The resulting amines, **7aa** and **7ca**, were then subjected to reductive cyclization using Zn in 6 M HCl, which afforded the desired pyrido[2,3-*d*]azepine **11aa** and pyrido[3,4-*d*]azepine **11ca** in yields of over 50% after chromatographic purification (32% and 33%, respectively, from **5**). A three-step approach in which the vinyl ethers **5aa** and **5ca** were converted into the corresponding dimethyl acetals **9**, which were then reduced to amines **10** before reductive cyclization of the latter, failed to improve on the two-step procedure, affording pyridoazepines **11aa** and **11ca** in 33% and 27% overall yields, respectively.

The originally envisaged route to 9-phenylpyrido[3,4-*d*]azepine (**11ba**) having being blocked by the failure of the attempted preparation of key intermediate **5ba** from **3b**, we decided to try coupling of **4a** to the pyridine ring of **2b** before homologation of its aldehyde



Scheme 3. Synthesis of 1-phenyl-3-pyridoazepines **11aa** and **11ca**.



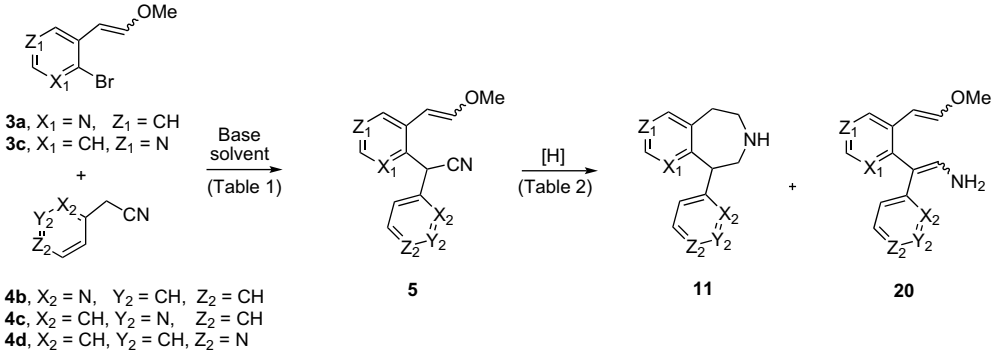
Scheme 4. The abandoned route to pyridoazepine **11ba**.

group. Accordingly, the aldehyde **2b** was protected as diethylacetal **12** by treatment with ethanol in the presence of triflic acid,[18] and the arylated nitrile **13** was obtained in 48% unoptimized yield by palladium-catalyzed coupling of **12** to phenylacetonitrile (Scheme 4). The rest of the synthesis of pyridoazepine **11ba** called for nitrile reduction, followed by protection of the amino group prior to hydrolysis of the acetal and one-carbon homologation. Sequential reduction of nitrile **13** provided amine **14**, which was subsequently protected with benzylchloroformate as carbamate **15**, but attempted cleavage of the acetal to the required aldehyde **16** led instead to tetrahydro-2,6-naphthyridine **17**, which was obtained in 82% yield as a separable mixture of the *cis* and *trans* stereoisomers **17a** (50%) and **17b** (32%).[19] No interconversion between **17a** and **17b** was observed in $CDCl_3$ solution after 4 days. When isomer **17a** was treated with (methoxymethylene)(triphenyl)phosphorane in THF in the presence of KO^{t}Bu or *n*-BuLi as base, a 7:3 mixture of **17a** and **17b** was obtained but no reaction with the small amount of free aldehyde **16** mediating this isomerization was observed. When a 3:2 mixture of the two stereoisomers was treated in the same way, only an approximately 1:1 mixture of **17a** and **17b** was obtained after 18 h. To avoid the formation of these undesired cyclic hemiaminals, we tried a different amine protector, refluxing **14** with phthalic anhydride in *o*-xylene to obtain a 30% yield of phthalimide **19** together with 4-phenyl-2,6-naphthyridine (**18**, produced in 21% yield by hydrolysis of the acetal followed by condensation with the unprotected amino group and aromatization). Unfortunately, attempts to hydrolyze the acetal group of **19** afforded only complex mixtures of products, and we made no further attempt to synthesize **11ba**.

2.2. Synthesis of 1-pyridyl-3-pyridoazepines

The protocols developed for **11aa** and **11ca** syntheses were extended to 1-pyridyl-3-pyridoazepines by coupling bromopyridines **3a** and **3c** to commercially available pyridylacetonitriles **4b**–**4d** and subjecting the resulting nitriles to reductive cyclization (Scheme 5).

Treatment of 2-bromo-3-[(*E*,*Z*)-2-methoxyvinyl]pyridine (**3a**) with 2-pyridylacetonitrile (**4b**) and NaH in THF at 80 °C provided nitrile **5ab** in 46% yield as mixture of *E* and *Z* isomers (Table 1, entry 1). Likewise, treatment with 3-pyridylacetonitrile (**4c**) and KO^{t}Bu in toluene gave a 72% yield of **5ac**, and in this case the mixture was separated chromatographically (Entry 2). Nitriles **5ad**, **5cc** and **5cd** were prepared similarly in yields ranging from 44% to 71% (Table 1, entries 3–5).[20]



Scheme 5. Synthesis of 1-pyridyl-3-pyridoazepines **11**.

Table 1
Preparation of diarylacetonitriles **5**

Entry	Bromopyridine[a]	Nitrile	Conditions	**5**[a] (% yield)	*E*:*Z* ratio[b]
1	**3a**	**4b**	NaH, THF, 80 °C, 22 h	**5ab** (46%)	1:1.8
2	**3a**	**4c**	KO^{t}Bu, toluene, 80 °C, 21 h	(*E*)-**5ac** (27%), (*Z*)-**5ac** (45%)	1:1.7
3	**3a**	**4d**	NaH, dioxane, 120 °C, 22 h	**5ad** (44%)	1:1.8
4	**3c**	**4c**	KO^{t}Bu, toluene, 80 °C, 20 h	**5cc** (71%)	1:1
5	**3c**	**4d**	NaH, dioxane, 120 °C, 20 h	**5cd** (51%)	1:1.8

[a] As mixtures of *E* and *Z* isomers, except for **5ac**, which was chromatographically separated.
[b] Determined by ^{1}H NMR.

Table 2
Reduction and cyclization of diarylacetonitriles **5**

Entry	Starting nitrile[a]	Conditions	Product (% yield)
1	**5ab**	Zn (51–127 equiv), $CoCl_2$ (7–16 equiv), 6 M HCl	—
2	**5ab**	LAH (10 equiv), $AlCl_3$ (10 equiv)	—
3	**5ab**	(1) DIBAL-H (7 equiv); (2) $NaBH_4$ (42 equiv)	—
4	(*Z*)-**5ac**	Zn (42 equiv), $CoCl_2$ (10 equiv), 6 M HCl	**11ac** (45%)
5	**5ad**	Zn (104 equiv), $CoCl_2$ (26 equiv), 6 M HCl	**11ad** (25%)
6	**5ad**	LAH (6 equiv), $AlCl_3$ (6 equiv)	**20ad** (70%)
7	**5ad**	(1) DIBAL-H (7 equiv); (2) $NaBH_4$ (42 equiv)	**20ad** (79%)
8	**5cc**	Zn (64 equiv), $CoCl_2$ (8 equiv), 6 M HCl	**11cc** (41%)
9	**5cd**	Zn (70 equiv), $CoCl_2$ (24 equiv), 6 M HCl	—
10	**5cd**	LAH (10 equiv), $AlCl_3$ (10 equiv)	**20cd** (16%)

[a] As mixtures of *E* and *Z* isomers, unless otherwise indicated.

The direct reductive cyclization of (*Z*)-**5ac**, **5ad**, and **5cc** (Zn, $CoCl_2$, 6 M HCl) afforded the corresponding azepines in modest isolated yields (Table 2, entries 4, 5, and 8). However, Zn/$CoCl_2$ treatment of nitriles **5ab** and **5cd** led to decomposition (entries 1 and 9), as did reduction of **5ab** with LAH/$AlCl_3$ or DIBAL-H/$NaBH_4$ (entries 2 and 3); while treatment of **5ad** and **5cd** with LAH/$AlCl_3$ or DIBAL-H/$NaBH_4$ afforded enamines (**20ad** and **20cd**) that under subsequent acid treatment yielded only intractable mixtures (entries 6, 7, and 10).

In conclusion, we have synthesized previously unreported 1-aryl-3-pyridoazepines from bromopyridines by reductive cyclization of (2-methoxyvinyl)pyridinyl(aryl)acetonitriles, which were easily derived from contiguously substituted bromo(2-methoxyvinyl)pyridines and the corresponding arylacetonitriles. The developed synthetic procedure allows a rapid entry to some pyrido[2,3-*d*]azepines and pyrido[3,4-*d*]azepines with phenyl and pyridinyl substituents at the azepine ring, although in the pyridinyl substituted series the final cyclization could not be achieved for all the targeted compounds.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250.13 and 62.89 MHz, respectively, using TMS as internal reference. All air-sensitive reactions were run under dried deoxygenated argon, in oven-dried glassware, with magnetic stirring; reagents were added by syringe through septa. All solvents for air or moisture-sensitive reactions were dried by standard procedures. All new compounds were chromatographically pure and both identity and homogeneity were provided by HRMS and by ^{1}H and ^{13}C NMR spectroscopy. All chemicals were purchased from Aldrich.

3.2. Typical procedure for vinylation of bromopyridines 2

*3.2.1. 2-Bromo-3-[(E,Z)-2-methoxyvinyl]pyridine (**3a**)*

A suspension of (methoxymethyl)triphenylphosphonium chloride (4.95 g, 14 mmol) in dry THF (20 mL) under Ar at 0 °C was treated with potassium *tert*-butoxide (2.03 g, 17.18 mmol). After stirring for 30 min a solution of aldehyde **2a** (2 g, 10.75 mmol) in THF (11 mL) was added. The mixture was further stirred at rt for 2 h, quenched with cold water, and extracted twice with ethyl acetate. The organic layers were combined, washed with water, evaporated under reduced pressure, and purified by flash chromatography (SiO_2, 1:9 EtOAc/hexane) to give colorless oil **3a** (2.04 g, 87%) as a (1:1) mixture of (*E*) and (*Z*) isomers. IR (neat) 1644, 1635, 1571, 1549, 1457, 1477 cm^{-1}. ^{1}H NMR δ 8.29 (dd, *J*=7.8, 1.9 Hz, 1H), 8.10 (dd, *J*=4.6, 1.9 Hz, 1H), 8.07 (dd, *J*=4.6, 1.9 Hz, 1H), 7.56 (dd, *J*=7.8, 1.9 Hz, 1H), 7.16 (dd, *J*=7.8, 4.6 Hz, 1H), 7.13 (dd, *J*=7.8, 4.6 Hz, 1H), 6.97 (d, *J*=12.9 Hz, 1H), 6.31 (d, *J*=7.2 Hz, 1H), 5.95 (d, *J*=12.9 Hz, 1H), 5.51 (d, *J*=7.2 Hz, 1H), 3.78 (s, 3H, OMe), 3.72 (s, 3H, OMe). ^{13}C NMR/DEPT δ 151.4 (CH), 150.8 (CH), 146.1 (CH), 145.9 (CH), 141.8 (C), 141.5 (C), 137.5 (CH), 133.4 (C), 132.6 (CH), 132.5 (C), 122.4 (CH), 122.2 (CH), 101.9 (CH), 101.6 (CH), 60.9 (OMe), 56.4 (OMe). MS (CI) (*m*/*z*): 244 [(M+2)+$C_2H_5^+$, 4], 242 (M+$C_2H_5^+$, 5), 216 [(M+2)+H$^+$, 33], 214 (M+H$^+$, 35). HRMS (ESI) calcd for C_8H_9BrNO [(M+H)$^+$] 213.9868, found 213.9850.

3.3. General procedure for arylation of arylacetonitriles 4

*3.3.1. Method A. {3-[(E,Z)-2-Methoxyvinyl]pyridin-2-yl}(phenyl)acetonitrile (**5aa**)*

To a mixture of 2-bromo-3-[(*E*,*Z*)-2-methoxyvinyl]pyridine (**3a**) (479 mg, 2.24 mmol) and potassium *tert*-butoxide (1.058 g, 8.95 mmol) in toluene (16 mL) was added phenylacetonitrile (540 μL, 4.45 mmol). The mixture was heated at 80 °C for 4 h. A saturated NH_4Cl aq solution was added (15 mL) and the mixture was extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, filtered, and the solvent evaporated. Purification by flash chromatography (SiO_2, 1:9 EtOAc/hexane) afforded oil **5aa** (241 mg, 43%) as a (1:1.4) mixture of (*E*) and (*Z*) isomers. IR (NaCl) 2245 (CN), 2185 (CN), 1644, 1563, 1494, 1453 cm^{-1}. ^{1}H NMR δ 8.49 (dd, *J*=4.8, 1.6 Hz, 0.4H), 8.46 (dd, *J*=4.7, 1.7 Hz, 0.6H), 8.14 (dd, *J*=7.9, 1.7 Hz, 0.6H), 7.58 (dd, *J*=7.9, 1.7 Hz, 0.4H), 7.42–7.28 (m, 5H), 7.27–7.18 (m, 1H), 6.81 (d, *J*=12.7 Hz, 0.4H), 6.25 (d, *J*=7.1 Hz, 0.6H), 5.73 (d, *J*=12.7 Hz, 0.4H), 5.57 (s, 0.6H), 5.56 (s, 0.4H), 5.19 (d, *J*=7.1 Hz, 0.6H), 3.74 (s, 1.8H), 3.52 (s, 1.2H). ^{13}C NMR/DEPT δ 151.9 (CH), 151.2 (C), 150.7 (C), 150.6 (CH), 147.2 (CH), 146.9 (CH), 137.8 (CH), 134.6 (C), 134.3 (CH), 130.6 (C), 129.4 (C), 129.0 (CH), 128.9 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 123.5 (CH), 123.0 (CH), 119.1 (CN), 118.8 (CN), 99.2 (CH), 98.9 (CH), 60.8 (OMe), 56.6 (OMe), 43.2 (CH), 42.8 (CH). MS (CI) (*m*/*z*): 279 (M+$C_2H_5^+$, 11), 251 (M+H$^+$, 100), 235 (8), 224 (11), 219 (7). HRMS (CI) calcd for $C_{16}H_{15}N_2O$ [(M+H)$^+$] 251.1178, found 251.1187.

*3.3.2. Method B. {3-[(E,Z)-2-Methoxyvinyl]pyridin-2-yl}(pyridin-2-yl)acetonitrile (**5ab**)*

A solution of 2-bromo-3-[(*E*,*Z*)-2-methoxyvinyl]pyridine (**3a**) (415 mg, 1.94 mmol) in THF (8 mL) was treated with NaH (388 mg, 9.7 mmol) followed by 2-(pyridin-2-yl)acetonitrile (**4b**) (428 μL, 3.97 mmol). The mixture was heated at 80 °C for 22 h. NH_4Cl aq solution was added (10 mL) and the mixture was extracted with CH_2Cl_2, washed with brine, dried, filtered, and the solvent evaporated. The residue was purified by flash chromatography (SiO_2, 98:2 CH_2Cl_2/MeOH) to afford oil **5ab** (224 mg, 46%) as (1:1.8) mixture of (*E*) and (*Z*) isomers. IR (neat) 2185, 2165 (CN), 1638, 1589 cm^{-1}. ^{1}H NMR δ 8.56–8.54 (m, 1H), 8.47–8.42 (m, 1H), 8.17 (dd, *J*=8.0, 1.5 Hz, 0.65H), 7.77–7.53 (m, 1.35H), 7.52–7.46 (m, 1H), 7.28–7.17 (m, 2H), 6.87 (d, *J*=12.7 Hz, 0.35H), 6.28 (d, *J*=7.1 Hz, 0.65H), 6.03 (d, *J*=12.7 Hz, 0.35H), 5.75 (s, 1H), 5.45 (d, *J*=7.1 Hz, 0.65H), 3.75 (s, 1.95H, OMe) 3.69 (s, 1.05H, OMe). ^{13}C NMR/DEPT δ 154.7 (C), 154.5 (C), 152.0 (C), 150.7 (CH), 150.0 (C), 149.4 (CH), 147.2 (CH), 146.8 (CH), 137.7 (CH), 137.3 (CH), 133.9 (CH), 131.2 (C), 129.9 (C), 123.6 (CH), 123.1 (CH), 123.0 (C), 122.9 (CH), 122.5 (CH), 120.1 (CH), 118.5 (C), 113.2 (CH), 99.3 (CH), 99.0 (CH), 60.8 (OMe), 56.5 (OMe), 46.0 (CH), 45.8 (CH). MS (CI) (*m*/*z*): 252

(M+H$^+$, 23), 241 (91), 225 (83), 221 (100), 183 (67). HRMS (CI) calcd for $C_{15}H_{14}N_3O$ [(M+H)$^+$] 252.1137, found 252.1136.

3.4. General procedure for the two-step reductive cyclization

*3.4.1. (2-{3-[(E,Z)-2-methoxyvinyl]pyridin-2-yl}-2-phenylethyl)amine (**7aa**)*

A solution of diisobutylaluminium hydride in hexane (1.7 M, 122 μL, 0.21 mmol) was added to a solution of **5aa** (25 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) at 0 °C and stirred for 30 min. Then the mixture was added to a suspension of sodium borohydride (157 mg, 4.1 mmol) in THF (1 mL) and methanol (2 mL) at 0 °C and stirred at rt for 30 min. Saturated aqueous ammonium chloride (10 mL) was added and stirring continued for 30 min, aqueous 10% NaOH (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried, concentrated in vacuo, and purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2/MeOH) to afford oil **7aa** (16 mg, 63%) as a (1:2.5) mixture of (*E*) and (*Z*) isomers. IR (NaCl) 3359 (NH_2), 1642, 1562, 1492, 1396 cm^{-1}. ^{1}H NMR δ 8.47 (dd, *J*=4.8, 1.7 Hz, 0.3H), 8.43 (dd, *J*=4.7, 1.7 Hz, 0.7H), 8.14 (dd, *J*=7.9, 1.7 Hz, 0.7H), 7.50 (dd, *J*=7.7, 1.7 Hz, 0.3H), 7.37–7.07 (m, 6H), 6.72 (d, *J*=12.8 Hz, 0.3H), 6.14 (d, *J*=7.1 Hz, 0.7H), 5.78 (d, *J*=12.8 Hz, 0.3H), 5.24 (d, *J*=7.1 Hz, 0.7H), 4.37–4.29 (m, 1H), 3.68 (s, 2.1H, OMe), 3.66–3.53 (m, 1H), 3.59 (s, 0.9H, OMe), 3.27–3.20 (m, 1H), 2.21 (br s, 2H). ^{13}C NMR/DEPT δ 157.3 (C), 150.5 (CH), 149.4 (CH), 146.3 (CH), 145.9 (CH), 142.0 (C), 141.8 (C), 136.9 (CH), 133.1 (C), 131.7 (CH), 130.6 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.5 (CH), 126.4 (CH), 121.6 (CH), 121.5 (C), 121.2 (CH), 100.7 (CH), 100.2 (CH), 60.6 (OMe), 56.3 (OMe), 52.9 (CH), 52.5 (CH), 47.3 (CH_2), 47.2 (CH_2). MS (CI) (*m*/*z*): 255 (M+H$^+$, 100), 238 (43), 226 (82), 209 (26), 194 (34), 180 (8). HRMS (CI) calcd for $C_{16}H_{19}N_2O$ [(M+H)$^+$] 255.1497, found 255.1497.

*3.4.2. 9-Phenyl-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine (**11aa**)*

Zn dust (200 mg, 3.06 mmol) was added to a solution of **7aa** (20 mg, 0.079 mmol) in 2 M HCl (0.7 mL) and the mixture was heated at 90 °C. After 30 min, additional quantities of 2 M HCl (0.7 mL) and Zn (200 mg, 3.06 mmol) were added and heating was continued for 30 min. After addition of 2 M NaOH until pH 9–11, the mixture was extracted with Cl_3CH, the organic layer was dried, concentrated in vacuo, and purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2/MeOH) to afford **11aa** (9 mg, 51%) as an oil. IR (NaCl) 3230, 1600, 1583, 1571, 1494 cm^{-1}. ^{1}H NMR δ 8.40 (dd, *J*=4.9, 1.7 Hz, 1H), 7.44 (dd, *J*=7.5, 1.7 Hz, 1H), 7.40–7.18 (m, 3H), 7.14–7.05 (m, 3H), 4.55 (dd, *J*=5.8, 2.2 Hz, 1H), 3.75 (dd, *J*=14.4, 5.8 Hz, 1H), 3.32 (dd, *J*=14.4, 2.2 Hz, 1H), 3.19–3.09 (m, 1H), 2.95–2.79 (m, 2H), 2.70–2.59 (m, 1H), 2.07 (br s, 1H). ^{13}C NMR/DEPT δ 162.4 (C), 146.5 (CH), 140.0 (C), 137.8 (CH), 136.9 (C), 128.4 (2×CH), 127.6 (2×CH), 125.9 (CH), 121.4 (CH), 56.5 (CH), 50.5 (CH_2), 47.6 (CH_2), 38.0 (CH_2). MS (EI) (*m*/*z*): 224 (M$^+$, 21), 196 (100), 180 (55), 167 (19), 152 (13), 133 (20). HRMS (EI) calcd for $C_{15}H_{16}N_2$ 224.1313, found 224.1307.

3.5. General procedure for the three-step reductive cyclization

*3.5.1. [3-(2,2-Dimethoxyethyl)pyridin-2-yl](phenyl) acetonitrile (**9aa**)*

To a stirred solution of **5aa** (212 mg, 0.848 mmol) in methanol (2 mL) at rt, Cl_2SO (187 μL, 2.5 mmol) was added. After stirring for 10 h, 2 M NaOH aqueous solution was added until pH 9–11 and the mixture was extracted with CH_2Cl_2, dried, filtered, and the solvent evaporated to afford **9aa** (234 mg, 98%) as an oil. IR (NaCl) 2250 (CN), 1659, 1632, 1350 cm^{-1}. ^{1}H NMR δ 8.55 (dd, *J*=4.7, 1.7 Hz, 1H), 7.54 (dd, *J*=7.8, 1.7 Hz, 1H), 7.38–7.25 (m, 5H), 7.21 (dd, *J*=7.8, 4.8 Hz, 1H), 5.79 (s, 1H), 4.26 (dd, *J*=6.5, 4.4 Hz, 1H), 3.30 (s, 3H, OMe), 3.29 (s, 3H, OMe), 2.94 (dd, *J*=14.3, 6.5 Hz, 1H), 2.78 (dd, *J*=14.3, 4.4 Hz, 1H). ^{13}C NMR/DEPT δ 153.9 (C), 148.0 (CH), 139.4 (CH), 134.8 (C), 130.2 (C), 128.9 (2×CH), 128.1 (CH), 127.8 (2×CH), 123.1 (CH), 119.3 (C), 104.9 (CH), 55.0 (OMe), 53.6 (OMe), 42.1 (CH), 36.0 (CH_2). MS (CI) (*m*/*z*) 311 (M+$C_2H_5^+$, 22), 283 (M+H$^+$, 88), 251 (100), 224 (45), 219 (14), 75 (35). HRMS (ESI) Calcd for $C_{17}H_{19}N_2O_2$ [(M+H)$^+$] 283.1440, found 283.1440.

*3.5.2. {2-[3-(2,2-Dimethoxyethyl)pyridin-2-yl]-2-phenylethyl}amine (**10aa**)*

To a solution of **9aa** (200 mg, 0.71 mmol) and $CoCl_2$ (95 mg, 0.71 mmol) in 2.5 mL of methanol at 0 °C, $NaBH_4$ (67 mg, 1.77 mmol) was added in small portions (caution: vigorous reaction with hydrogen evolution). The immediate formation of a black precipitate was observed, and the mixture was stirred for an additional 1 h. 10% aqueous HCl was added until pH 3–4 and, after stirring for 2 min, the pH was adjusted to 10 with 4 M NaOH, and the mixture was extracted with Cl_3CH. The combined organic layers were dried, filtered, and concentrated to give a residue, which was purified by flash chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) to afford **10aa** (144 mg, 71%) as an oil. IR (neat) 3366, 3303, 1673, 1572, 1492 cm^{-1}. ^{1}H NMR δ 8.38 (dd, *J*=4.7, 1.5 Hz, 1H), 7.34 (dd, *J*=7.7, 1.6 Hz, 1H), 7.12–6.94 (m, 6H), 4.23 (dd, *J*=8.3, 5.6 Hz, 1H), 3.92 (dd, *J*=6.4, 4.6 Hz, 1H), 3.47–3.39 (m, 1H), 3.10–3.01 (m, 1H), 3.03 (s, 6H, 2×OMe), 2.75 (dd, *J*=14.4, 6.4 Hz, 1H), 2.57 (dd, *J*=14.4, 4.6 Hz, 1H), 1.77 (br s, 2H, NH_2). ^{13}C NMR/DEPT δ 159.4 (C), 146.7 (CH), 141.8 (C), 138.5 (CH), 131.4 (C), 128.2 (2×CH), 128.1 (2×CH), 126.2 (CH), 121.1 (CH), 104.2 (CH), 53.9 (OMe), 53.2 (OMe), 52.3 (CH), 47.3 (CH_2), 35.3 (CH_2). MS (CI) (*m*/*z*): 315 (M+$C_2H_5^+$, 13), 287 (M+H$^+$, 100), 255 (70), 240 (31), 223 (12). HRMS (ESI) calcd for $C_{17}H_{23}N_2O_2$ [(M+H)$^+$] 287.1750, found 287.1740.

*3.5.3. 9-Phenyl-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine (**11aa**)*

Zn dust (165 mg, 2.5 mmol) was added to a solution of **10aa** (40 mg, 0.14 mmol) in 2 M HCl (1 mL) and the mixture was heated at 90 °C for 2 h. After addition of 2 M NaOH until pH 9–11, the mixture was extracted with Cl_3CH, the organic layer was dried, concentrated in vacuo, and purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2/MeOH) to afford **11aa** (15 mg, 47%) as an oil.

3.6. General procedure for the one-pot reductive cyclization

*3.6.1. 9-Phenyl-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine (**11aa**)*

Zn dust (200 mg, 3.06 mmol) and $CoCl_2$ (50 mg, 0.39 mmol) were added to a solution of **5aa** (20 mg, 0.08 mmol) in 6 M HCl (0.7 mL) and the mixture was heated at 90 °C. After 20 min, additional quantities of 6 M HCl (0.7 mL), Zn dust (200 mg, 3.06 mmol), and $CoCl_2$ (50 mg, 0.39 mmol) were added and heating was continued for 20 min. After addition of 2 M NaOH until pH 9–11, the mixture was extracted with Cl_3CH, the organic layer was dried, concentrated in vacuo, and purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2/MeOH) to afford **11aa** (7 mg, 39%) as an oil.

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Supplementary data

Experimental procedures and characterization data for all reported compounds, and copies of the ^{1}H NMR and ^{13}C NMR/DEPT

spectra for all new compounds are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.075.

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20. The missing combination (reaction of **3c** with **4b**) was not attempted.