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A single step synthesis of 6-aminophenanthridines from anilines and 2-chlorobenzonitriles

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Abstract—Biologically active 6-aminophenanthridines were prepared in a single step procedure: Metal amides in liquid ammonia promoted the condensation of anilines with 2-chloro-benzonitriles. 6-Aminophenanthridines were isolated in moderate yield.

1. Introduction

Prion deseases are neurodegenerative pathologies that include Creutzfeld–Jakob in human, bovine spongiform encephalopathie in cattle and scrapie in sheep. All these disorders are associated with an abnormal conformation of the normal host protein PrP.[1]

Up to now no treatment has demonstrated clinical usefulness.[2] Very recently, we have developed a rapid yeast-based assay to screen for antiprion drugs, which led to the discovery of phenanthridines as new prion inhibitors. In particular, 6-aminophenanthridines (6-AP) displayed the highest inhibition.[3] In our test, 6-APs were found more active than other previously reported inhibitors.[4]

This prompts us to study the preparation of these heterocycles. Phenanthridines can be obtained by cyclisation of various biphenyles: 2-formyl-2′-nitrobiphenyle,[5] 2′iodo-2-isocyanobiphenyle.[6] Other syntheses include cyclisation of *N*-benzylanilides by reaction of hypervalent iodine,[7] condensation of Boc-aniline with 2-chlorobenzaldimines under basic conditions[8] and annelation of tetrahydroquinolin-4-one.[9]

In contrast to the numerous approaches to phenanthridines, very few reports deal with 6-APs. The main routes start from phenanthridinones. Phenanthridinones can be obtained from phenanthridines via rearrangement of the *N*-oxide,[10] from fluorenones by the Schmidt reaction[11] and by Suzuki coupling of 2-Bocaminophenylboronic acid with 2-bromobenzoates.[12] After conversion of phenanthridinone into 6-chlorophenanthridines,[13] 6-AP could then be obtained upon reaction with ammonia.[14]

Recently, a one step synthesis of 6-substituted-phenanthridine has been described. It is based on the condensation of 2 arynes generated from fluoroarenes with one equivalent of nitrile. However this approach does not allow the introduction of various groups on the benzene rings and cannot be applied to the synthesis of unsubstituted 6-amino groups.[15]

2. Results and discussion

2.1. Amination of 6-chlorophenanthridines

At the onset of our work, we tried to prepare 6-APs via 6-chlorophenanthridine[16] using the above mentioned previously reported procedure: 6-chlorophenanthridine was obtained in an overall 48% yield from phenanthridine but exposure to a methanolic solution of ammonia produced only a minor trace of 6-AP. The amination was then successfully achieved by hydrogenation of 6-benzylaminophenanthridine prepared by refluxing 6-chlorophenanthridine in benzylamine (Scheme 1).

2.2. Cyclization of 2-chlorophenylbenzamidine

However, this classical approach was limited. We needed to prepare functionalised 6-APs in order to establish structure–activity relationships. This led us to investigate other routes.

Taking into account that potassium amide in liquid ammonia allowed the cyclisation of the imine of

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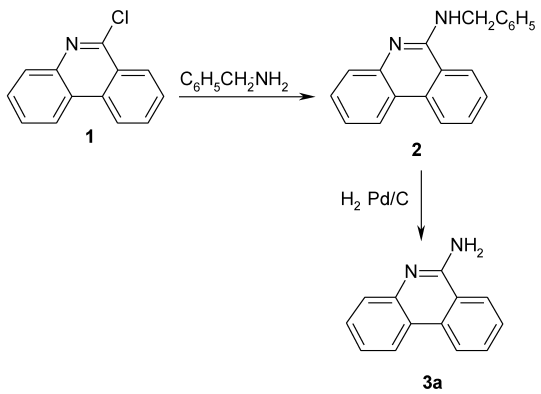
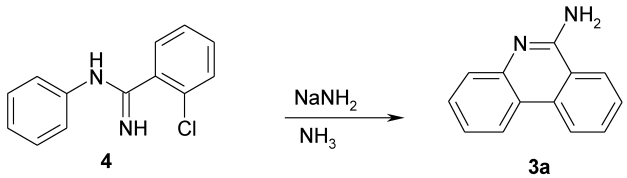


Scheme 1. Amination of 6-chlorophenanthridine.

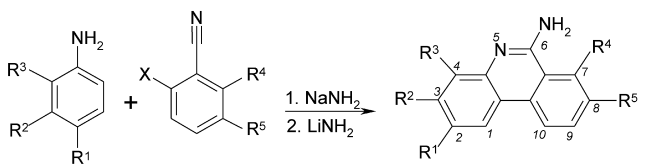
2-chlorobenzaldehyde with naphthylamine into benzo[*c*]-phenanthridine,[17] we have experimented the cyclisation of *N*-phenyl-2-chlorobenzamidine **4**. Addition of the amidine **4** to a sodium amide suspension in liquid ammonia led to the formation of 6-AP **3a** which was separated from unreacted **4** by column chromatography (Scheme 2).



Scheme 2. Cyclisation of 2-chlorophenylbenzamidine.

2.3. Direct condensation of arylamines with 2-halonitriles

In order to get the target compounds in a one step procedure, we have studied the condensation of 2-halobenzonitriles with aryl amines in the presence of several combination of bases: The use of a mixture of sodium and lithium amide was found the most efficient providing single step access to 6-APs. An attempt to use 2-fluorobenzonitrile instead of 2-chlorobenzonitrile was unsuccessful (Scheme 3, Table 1).

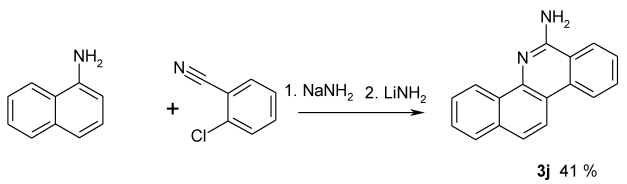


Scheme 3. Condensation of anilines with 2-chlorobenzonitriles.

Table 1. Phenanthridines produced via Scheme 3

Entry	Compounds **3**	R^1	R^2	X	R^3	R^4	R^5	Yield (%)
1	**3a**	H	H	Cl	H	H	H	42
2	**3b**	F	H	Cl	H	H	H	39
3	**3c**	OCH_3	H	Cl	H	H	H	52
4	**3d**	H	F	Cl	H	H	H	44
5	**3e**	H	H	Cl	H	H	Cl	38
6	**3f**	H	H	Cl	H	H	CF_3	36
7	**3g**	OCH_3	H	Cl	OCH_3	H	H	62
8	**3h**	H	H	Cl	H	Cl	H	17
9	**3i**	F	H	Cl	H	H	Cl	33

Similarly, naphthylamine reacted with 2-chlorobenzonitrile to afford the benzo[*c*]phenanthridine **3j** (Scheme 4).



Scheme 4. Preparation of benzo[*c*]phenanthridine.

3. Conclusion

Although the isolated yields of 6-APs were moderate, the presented procedure is simple to carry out, it allowed us to prepare a series of diversely substituted 6-APs, bearing either electro-donating or electro-attractive groups on the aromatic rings.

Efforts are underway to use these easily obtainable 6-APs as synthetic intermediates to prepare other biologically active phenanthridines. Further, the obtention of compound **3j** illustrate the potency of the approach in the preparation of benzophenanthridines which display a broad range of pharmacological activities.[19–21]

4. Experimental

4.1. General

All the starting material used were commercially available except 6-chlorophenanthridine prepared from phenanthridine. ^{1}H and ^{13}C NMR were recorded on a Bruker 400 MHz spectrometer. Structural assignments were achieved by 1D and 2D methods.

4.1.1. 6-Benzylaminophenanthridine (2) from 6-chlorophenanthridine (1). A solution of 6-chlorophenanthridine **1** (4.5 g, 21.1 mmol) in benzylamine 15 mL and tributylamine 2 mL was refluxed 3 h. After concentration under reduced pressure, the residue was chromatographed on silica gel using CH_2Cl_2 containing 0.1% NEt_3 as eluent.

Yield 86%; mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 4.97 (s, 2H, CH_2–C_6H_5); 5.6 (br s, 1H, NH); 7.35 (t, 1H, 2-H); 7.32 (t, 1H, H-8); 7.4 and 7.55 (2m, 5H, C_6H_5); 7.58 (t, 1H,); 7.62 (t,); 7.78 (t, 1H,); 7.82 (t, 1H,); 7.85 (d, 1H, 7-H); 8.37 (d, 1H, 1-H); 8.55 (d, 1H, 10-H). Analysis: calculated for $C_{20}H_{16}N_2$: C, 84.48; H 5.67%; N 9.85%; found: C, 84.35; H 5.81%; N 10.02%.

4.1.2. Debenzylation of 6-benzylaminophenanthridine (2) into 6-aminophenanthridine (3a). To a solution of 6-benzylaminophenanthridine **2** (2.84 g, 10 mmol) in EtOH–AcOH (100 mL, 95:5) was added 5% Pd–C (0.1 g). The mixture was hydrogenated under vigorous stirring (5 atm, 40 °C) for 3 h. After removal by filtration of the catalyst, the solution was concentrated under reduced pressure, diluted in 100 mL H_2O, brought to pH 10 with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The remaining solid crystallized upon trituration with AcOEt.

Yield 19%; mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (t, 1H, J_{1-2}=J_{2-3}=8.6 Hz, 2-H); 7.58 (t, 1H, J_{7-8}=J_{8-9}=8.5 Hz, 8-H); 7.64 (t, 1H, J_{3-4}=8.6 Hz, 3-H); 7.72 (d, 1H, 4-H); 7.82 (t, 1H, J_{9-10}=8.5 Hz, 9-H); 7.95 (d, 1H, 7-H); 8.38 (d, 1H, 1-H); 8.56 (d, 1H, 10-H) Analysis: calculated for $C_{13}H_{10}N_2$: C, 80.39%; H 5.19%; N 14.42%; found: C, 80.09%; H 5.31%; N 14.56%.

4.1.3. *N*-Phenyl-2-chlorobenzamidine (4). The method used by Daoust and Lessard[18] for the synthesis of phenylbenzamidine was slightly modified: To a solution aniline in 20 mL, toluene, $NaNH_2$ (0.39 g, 10 mmol) was added. After 1h stirring at 50 °C, 2-chlorobenzonitrile was added and the mixture brought to reflux for 2 h. After cooling to 0 °C, NH_4Cl, then water 100 mL were added carefully and the mixture extracted with 3×100 mL CH_2Cl_2. The organic solution was washed with water, dried (Na_2SO_4) and concentrated under reduce pressure. The amidine crystallized from Et_2O as a dark brown solid. Yield 55%; mp 170 °C; ^{1}H NMR ($CDCl_3$) δ 4.80 (br s, 1H, NH); 6.95 (m, 3H, Aro); 7.40 (m, 5H, Aro); 7.45 (d, 1H, Aro); 7.60 (br s, 1H, NH). MS (ES^+) $C_{13}H_{11}N_2Cl$ requires 230 and 232 found: 231, 233 ($M+H^+$, 100%).

4.1.4. Aminophenanthridine 3a from 4. In a flask connected with an efficient condenser, ammonia (100 mL) was introduced followed by $Fe(NO_3)_3$ (0.02 g) and piece by piece Na (1.15 g, 50 mmol). The solution was stirred for 0.5 h during this period, the initial blue colour of the solution of Na gradually turned to grey indicating the complete conversion into $NaNH_2$. *N*-Phenyl-2-chlorobenzamidine **4** was introduced. After 2 h stirring, NH_4Cl (5 g) was added gradually and the mixture was left overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried and evaporated. The mixture was applied to a silica gel column and eluted with CH_2Cl_2 then CH_2Cl_2–MeOH (99:1) containing 0.5% NEt_3 as eluent. Unreacted **4** (yield: 22%) was eluted first followed by **3a** (yield 56%).

4.2. Preparation of 6-aminophenanthridines (3) from arylamines and 2-halonitriles

The preparation of the $NaNH_2$ suspension was carried out as described above. To a suspension of $NaNH_2$ in liquid NH_3 (10 mmol, 100 mL) the arylamines **1** in anhydrous Et_2O (10 mmol, 30 mL) were added droplet. The mixture was stirred for 0.5 h. After this time, 2-halobenzonitriles were gradually added. In most cases, the 2-chlorobenzonitriles were added as solids, (2-chlorobenzonitrile was added in anhydrous Et_2O). The mixture was then stirred for 2 h and lithium (0.14 g, 20 mmol) was added in two pieces. The mixture was stirred an additional 2 h, NH_4Cl (2 g) was then added carefully. The reaction was left overnight. After evaporation of ammonia, work up and purification were performed as described above. 6-APs were easily distinguished from benzimidine by their stronger UV absorption on tlc plates. Products **3** were crystallized from AcOEt.

4.2.1. 6-Amino-2-fluorophenanthridine (3b). Mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 5.70 (br s, 2H, NH_2); 7.3 (dd, 1H, $J_{3\text{-F}}$=10.1 Hz, J_{1-3}=2.5 Hz, 3-H); 7.65 (t, 1H, J_{8-9}=J_{9-10}=8.5 Hz, 8-H) 7.68 (t, 1H, 3-H); 7.75 (t, 1H, 9-H); 7.85 (d, 1H, 7-H); 7.94 (dd, 1H, 1-H); 8.35 (d, 1-H, 10-H). Analysis: calculated for $C_{13}H_9FN_2$: C, 73.57%; H, 4.27%; N, 13.20%; found: C, 73.76%; H, 4.12%; N, 13.31%.

4.2.2. 6-Amino-2-methoxyphenanthridine (3c). Mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3); (5.20 (br s, 2H, NH_2); 7.12, dd, J_{3-4}=8.5 Hz, J_{1-3}=2 Hz, 3-H); 7.60 (t, 1H, 8-H); 7.66 (d, 1H, 1-H); 7.69 (d, 1H, 4-H); 7.80 (t, 1H, 9-H); 7.95 (d, 1H, 7-H); 8.42 (d, 1H, 10-H). Analysis: calculated for $C_{14}H_{12}N_2O$: C, 74.98%; H, 5.39%; N, 12.49%; found: C, 74.81%; H, 5.45%; N, 12.77%.

4.2.3. 6-Amino-3-fluorophenanthridine (3d). Mp 182–183 °C; ^{1}H NMR ($CDCl_3$) δ 5.75 (br s, 2H, NH_2); 7.15, (td, 1H, $J_{2\text{-F}}$=10.2 Hz, J_{2-4}=2.7 Hz, 2-H); 7.4 (dd,1H, $J_{4\text{-F}}$=10.2 Hz, 4-H); 7.65 (t, 1H, J_{7-8}=J_{8-9}=8.2 Hz, 8-H); 7.84 (t, 1H, J_{9-10}=8.2 Hz, 9-H); 7.94 (d, 1H, 7-H); (8.35, dd, J_{1-2}=8.9 Hz, J_{1-3}=1 Hz, 1-H); 8.48 (d, 1H, 10-H). ^{13}C: 111.5 (d, $J_{3\text{-F}}$=23.3 Hz, C-3); 112.4 (d, $J_{2\text{-F}}$=23.4 Hz, C-2); 123.10, C-10; 123.9, C-7, 124.27 (d, $J_{1\text{-F}}$=8 Hz); 127.51, C-7); 131.40, C-9; 147 (d, J_{C-F}=12 Hz, C_4–*C*–N) 155.89, C-2; 163.22 (d, $J_{3\text{-F}}$=243 Hz, C-3). Analysis: calculated for $C_{13}H_9FN_2$: C, 73.57%; H, 4.27%; N, 13.20%; found: C, 73.41%; H, 4.38%; N, 13.43%.

4.2.4. 6-Amino-8-chlorophenanthridine (3e). Mp 175–180 °C; ^{1}H NMR ($CDCl_3$) δ 6.60 (br s, 2H, NH_2); 7.35 (t, 1H, J_{2-1}=J_{2-3}=8.4 Hz, 2-H); 7.55 (t, 1H, 3-H); 7.65 (d, 1H, J_{3-4}=8.4 Hz, H-4); 7.72 (dd, 1H, J_{9-10}=8 Hz, J_{7-9}=2 Hz, 9-H); 8.18 (d, 1H, 7-H); 8.32 (d, 1H, 1-H); 8.65 (d, 1H, 10-H). Analysis: calculated for $C_{13}H_9ClN_2$: C, 68.28%; H, 3.97%; N, 12.25%; found: 68.44%; H, 4.11%; N, 12.35%.

4.2.5. 6-Amino-8-trifluoromethylphenanthridine (3f). Mp 146–149 °C; ^{1}H NMR ($CDCl_3$) δ 6.60 (br s, 2H, NH_2); 7.35 (t, 1H, J_{1-2}=J_{2-3}=8.3 Hz, 2-H); 7.55 (t, 1H, J_{3-4}=8.3 Hz, 3-H); 7.65 (d, 1H, 4-H); 7.95 (dd, J_{7-9}=2 Hz, 1H, 9-H); 8.15 (d, 1H, J_{7-9}=2 Hz, H-7); 8.32 (d, 1H, 1-H); 8.65 (d, 1H, 10-H). Analysis: calculated for $C_{14}H_9F_3N_2$: C, 64.12%; H, 3.46%; N, 10.68%; found C, 64.10%; H, 3.31%, N, 10.81%.

4.2.6. 6-Amino-2,4-dimethoxyphenanthridine (3g). Mp 138–141 °C; ^{1}H NMR ($CDCl_3$) δ 4.00 and 4.05 (2s, 2×3H, $2OCH_3$); 5.5 (br s, 2H, NH_2); 6.70 (d, 1H, J_{1-3}=2 Hz, 3-H); 7.38 (d, 1H, 1-H); 7.69 (t, 1H; J_{7-8}=J_{8-9}=8.4 Hz, 8-H); 7.82 (t, 1H, 9-H); 8.02 (d, 1H, 7-H) 8.50 (d, 1H, H-10). Analysis: calculated for $C_{15}H_{14}N_2O_2$: C, 70.85%; H, 5.55%; N, 11.02%, found: C, 70.65%; H, 5.45%; N, 10.78%.

4.2.7. 6-Amino-7-chlorophenanthridine (3h). Mp 156–157 °C; ^{1}H NMR ($CDCl_3$) δ 6.37 (br s, 2H, NH_2); 7.37 (t, 1H, J_{2-1}=J_{2-3}=8.3 Hz, 2-H); 7.60 (t, 1H, 3-H); 7.65 (m, 3H, 4-H+8-H+9-H); 8.31 (d, 1H, 1-H); 8.54 (m, 1H, 10-H). Analysis: calculated for $C_{13}H_9ClN_2$: C, 68.28%; H, 3.97%; N, 12.25%; found: C, 68.44%; H, 4.19%; N, 12.17%.

4.2.8. 6-Amino-8-chloro-2-fluorophenanthridine (3i). Mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 5.70 (br s, 2H, NH_2); 7.30 (dd, 1H, $J_{2\text{-F}}$=10 Hz, J_{2-1}=8 Hz, 2-H); 7.55 (dd, 1H, 4-H); 7.67 (td, 1H, 9-H); 7.87 (d, 1H, *J*=2 Hz, 7-H) 7.98 (dd,

1-H); 8.35 (d, 1H, 10-H). Analysis: calculated for $C_{13}H_8ClFN_2$: C, 63.30%; H, 3.27%; N, 11.36%; found C, 63.30%; H, 3.15%; N, 11.45%.

4.2.9. 8-Amino-benzo[*c*]phenanthridine (3j). Mp 145–150 °C; ^{1}H NMR ($CDCl_3$) δ 5.45 (br s, 2H, NH_2); 7.50–8.00 (m, 7H); 8.30 (d, 1H); 8.70 (d, 1H); 9.20 (d, 1H). Analysis: calculated for $C_{17}H_{12}N_2$: C, 83.58%; H, 4.95%; N, 11.47%; found C, 83.33%; H, 5.12%; N, 11.23%.

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