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An expeditious synthesis of 6-aminophenanthridines

Fabienne Gug,[a] Marc Blondel,[b] Nathalie Desban,[b] Serge Bouaziz,[c] Jean-Michel Vierfond[a] and Hervé Galons[a,*]

[a]*Laboratoire de Chimie Organique, INSERM U 648, Université René Descartes, 4, avenue de L'Observatoire, 75006 Paris, France*
[b]*Amyloid and Cell Cycle Group, Station Biologique du CNRS, place G. Teissier, 29680 Roscoff, Bretagne, France*
[c]*UPCG, INSERM U640, CNRS UMR 8151, Université René Descartes, 4, avenue de L'Observatoire, 75006 Paris, France*

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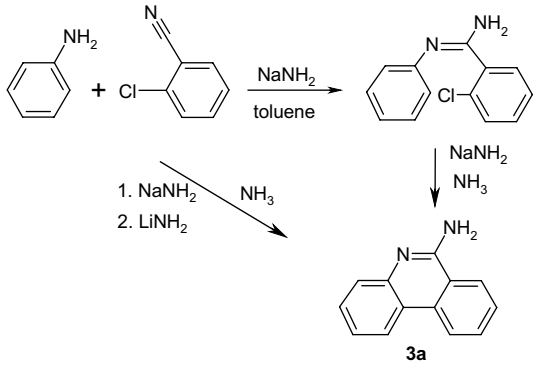
Abstract—A simple synthesis of biologically active 6-aminophenanthridines was achieved by a Suzuki–Miyaura coupling reaction. Condensation of 2-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)aniline with 2-chlorobenzonitriles afforded 6-aminophenanthridines useful as prions inhibitors in a mild one-step procedure. The intermediate 2-amino-2′cyanobiphenyls could not be isolated.

1. Introduction

Prion related diseases or transmissible spongiform encephalopathies form a group of neurodegenerative diseases that includes scrapie (sheep), mad cow disease and Creutzfeldt-Jacob disease in human. According to the 'protein only' hypothesis formulated by Stanley Prusiner, prions are infectious proteins.[1] A high throughput screening of anti-prions drugs based on the inhibition of yeast prions replication has been developed and allowed to select phenanthridine and some of its derivatives as new prions inhibitors. In particular 6-aminophenanthridines (6APs) were found to be potent inhibitors of yeast prions and, in addition, their activity against mammalian prions were established in cell-based assays.[2]

Very few studies have been devoted to the preparation of 6APs. We have previously reported a one step synthesis of 6APs, which relies on the condensation of 2-chlorobenzonitriles on anilines via the formation of an intermediate amidine (Scheme 1).[3] This synthesis is economical and allowed us to prepare very active compounds. However, the yields were moderate or low and the procedure requires the use of anhydrous liquid ammonia as solvent. More importantly, derivatives substituted in position 9 and 10 could not be obtained.



Scheme 1. Condensation of 2-chlorobenzonitriles with anilines promoted by alkali metals amides.

Indeed, the cyclisation of the intermediate amidine requires an hydrogen *ortho* to the halogen as benzyne are presumed intermediates. Also, *para*-substituted 2-chlorobenzonitriles failed to react under these conditions.

Structure–activity studies showed that derivatives bearing various groups introduced in position 1–4 of the 6-AP reduced the activity whereas electron-withdrawing groups (Cl or CF_3) in position 8 increased the anti-prion activity strongly suggesting the potential interest of products substituted in positions 9 and 10.

We now report a one step process to 6-APs based on a Suzuki–Miyaura coupling.[4] A large amount of work

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* Corresponding author. Tel.: +33 15373 9684; fax: +33 14329 0592; e-mail: herve.galons@univ-paris5.fr

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has been devoted to the choice of the catalyst and reaction conditions. Several directions have been pursued: polymer supported,[5] incarcerated[6] or water soluble[7] phosphine ligands have been proposed in various combination of base and solvent.[8] Tetrapodal phosphines, were particularly efficient exhibiting substrate–catalyst ratios up to 100,000.[9] Several attractive conditions, which avoid the use of oxygen-sensitive phosphines have also been found effective using primary,[10] secondary,[11] tertiary[12] amines or ammonium[13] ligands. Even palladium on activated carbon was successfully used however the reaction was conducted at high temperature.[14]

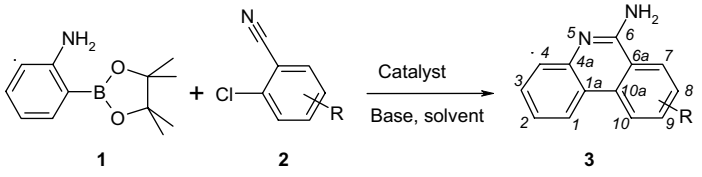
All these studies have been achieved with boronic acids, which are considered more reactive than boronic esters.[15,16] We envisioned to prepare 6-APs starting from commercially available 2-chlorobenzonitriles and 2-aminophenylboronic esters.[17] Very few reports have detailed the influence of base and catalyst when Suzuki coupling are conducted with boronic esters. However, on a practical point of view, the use of boronic esters offers several advantages. In particular, they are soluble and stable in organic solvents,[18] they were stored in organic solutions, which facilitated the optimisation studies and, when unreacted, they can be recovered by column chromatography. We focused our attention on the preparation 6-amino-8-chloro-phenanthridine **3b** one of the most active inhibitor to date. The condensation of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline with 2,5-dichlorobenzonitrile was studied (Scheme 2) using various experimental conditions (Table 1). Palladium-tetrakistriphenylphosphine $Pd[P(C_6H_5)_3]_4$ was first used and compared with a series of reaction conditions using Pd on carbon or palladium II acetate.

The use of a bulky[21] primary amine: adamantanamine (simply added as the commercially available hydrochloride) afforded **3b** in good yield upon heating in 1,2-dimethoxyethane or dioxane.

The selected conditions were then used to prepare other derivatives (e.g., unknown 9- and 10-substituted 6-aminophenanthridines) (Table 1, entries 10–13).[20] It can be noticed that phenanthridines[22] and phenanthridinones[23] have been previously obtained by Suzuki coupling using 2-Bocaminophenylboronic acid. Acidic cleavage of the Boc group was required to allow cyclisation.

2. Conclusion

A simple access to biologically active 6-APs is described. Among the newly prepared compounds, 6-amino-9-fluorophenanthridine **3d** was found slightly more active than **3b**. In all cases under study the intermediate biphenyls could not be isolated in the reaction mixture. More generally optimised cross-coupling conditions described herein could be useful for the condensation of other sterically hindered boronic esters and arylchlorides.



1 2 3

Scheme 2. Condensation of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline with 2-chlorobenzonitriles.

Table 1. 6-Aminophenanthridines prepared

Entry	Conditions: catalyst (mol equiv), solvent, ligand (mol equiv), base (mol equiv),[a] temp, time	3	R	Yield[b] (%)
1	$Pd[P(C_6H_5)_3]_4$ (0.03), dimethoxyethane, 2 N Na_2CO_3 (2), 80 °C, 12 h	**3b**	8-Cl	25
2	Pd–C (0.01), *N*-methylpyrrolidone, 2 N Na_2CO_3 (2), 100 °C, 16 h	**3b**	8-Cl	0
3	$Pd(OAc)_2$ (0.05), dimethoxyethane, 2 N Na_2CO_3 (2), 80 °C, 16 h	**3b**	8-Cl	Traces
4	$Pd(OAc)_2$ (0.05), THF, 2 N Na_2CO_3 (2.2),[e] $AdNH_2$·HCl (0.2), 70 °C, 16 h	**3b**	8-Cl	5
5	$Pd(OAc)_2$ (0.05), dimethoxyethane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 90 °C, 16 h	**3b**	8-Cl	63
6	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3b**	8-Cl	73, 69,[c] 45[d]
7	$Pd(OAc)_2$ (0.05), dioxane, 2 N Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3b**	8-Cl	60
8	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 20 °C, 48 h	**3b**	8-Cl	0
9	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3a**	H	65
10	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3c**	9-O-$CH_2C_6H_5$	52
11	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3d**	9-F	77
12	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3e**	9-Cl	81
13	$Pd(OAc)_2$ (0.05), dioxane, Cs_2CO_3 (2.2), $AdNH_2$·HCl (0.2), 100 °C, 16 h	**3f**	10-Cl	76

[a] Other bases (*t*-BuOK, K_2CO_3) were used without success.
[b] Determined by HPLC, mean of at least two experiments.
[c] Isolated by column chromatography.
[d] Isolated by crystallisation.
[e] $AdNH_2$·HCl = adamantanamine hydrochloride. Compounds **2** were commercially available except 2-chloro-4-benzyloxy-benzonitrile[19] used in the synthesis of **3c**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.135. Analytical data of new compounds.

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19. Prepared in 66% yield from 2-chloro-4-hydroxybenzonitrile: by a Mitsunobu procedure, crystallisation from cyclohexane. Mp: 98–100 °C. ^{1}H NMR ($CDCl_3$): δ 5.11 (s, 2H); 6.94 (dd, 1H); 7.10 (d, 1H); 7.40 (br s, 5H); 6.55 (d, 1H).
20. Typical procedure for the synthesis of 6APs (entries 6, 8–13). Solvents were deaerated with nitrogen and a slow bubbling of nitrogen was maintained throughout the reaction. $Pd(OAc)_2$ (0.112 g, 0.5 mmol) was added to a solution of 2-chlorobenzonitriles **2** (10 mmol) in dioxane (75 mL). After stirring for 5 min at rt 1-adamantanamine hydrochloride (0.76 g, 4 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.39 g, 11 mmol) and Cs_2CO_3 (0.7 g, 22 mmol) were added. The reaction was stirred 16 h at 100 °C. After cooling to rt the mixture was concentrated in vacuo to half of its initial volume and partitioned between CH_2Cl_2 and water. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated until dryness. The mixture was chromatographed on silica gel using CH_2Cl_2–EtOH 0.5–>5% + NEt_3 0.5%.
Compound **3a**: mp (AcOEt) 186–188 °C, lit.[3] 189 °C.
Compound **3b**: mp (AcOEt) 177–181 °C, lit.[3] 180 °C.
Compound **3c**: mp (AcOEt) 112–115 °C; ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, CH_2); 6.3 (br s, 2H, NH_2); 7.32 (dd, J_{8-7} = 8.1 Hz, J_{10-8} = 2 Hz, 1H, 8-H); 7.39 (t, 1H, $J_{2-1} = J_{2-3}$ = 8.3 Hz, 2-H); 7.44 (m, 5H, C_6H_5); 7.58 (t, 1H, J_{3-4} = 8.3 Hz, 3-H); 7.72 (d, 1H, 4-H); 7.96 (d, 1H, 10-H); 8.10 (d, 1H, 7-H); 8.26 (d, 1H, 1-H).
Compound **3d**: mp (AcOEt) 142–145 °C; ^{1}H NMR ($CDCl_3$): δ 5.55 (s large, 2H, NH_2); 7.42 (t, 1H, $J_{6-7} = J_{7-8}$ = 8.2 Hz, 7-H); 7.45 (t, 1H, $J_{2-1} = J_{2-3}$ = 8.23 Hz, 2-H); 7.65 (t, 1H, 3-H); 7.75 (d, 1H, 4-H); 7.97 (dd, 1H, $J_{8\text{-F}}$ = 10 Hz, 8-H); 8.17 (d, 1H, $J_{10\text{-F}}$ = 9.9 Hz, 10-H).
Compound **3e**: mp (AcOEt) 131–133 °C; ^{1}H NMR ($CDCl_3$): δ 5.55 (br s, 2H, NH_2); 7.43 (td, 1H, $J_{1-2} = J_{2-3}$ = 8.2 Hz, J_{2-4} = 1.0 Hz, 2-H); 7.60 (d, 1H, 8-H); 7.65 (td, 1H, 3-H); 7.74 (dd, 1H, 4-H); 7.92(d, 1H, J_{7-8} = 8.53 Hz, 7-H); 8.30 (dd, 1H, 1-H); 8.51 (d, 1H, J_{8-10} = 1.71 Hz, 10-H). ^{13}C NMR ($CDCl_3$): 116.8 (6a-C); 120 (1a-C); 122.1 (1-C); 122.6 (10-C); 123.7 (2-C); 125.1 (7-C); 126.1 (4-C); 127.7 (8-C); 129.9 (3-C); 135.6 (10a-C); 137.0 (9-C); 144.0 (4a-C); 154.2 (6-C).
Compound **3f**: mp (AcOEt) 127–129 °C; ^{1}H NMR ($CDCl_3$): δ 5.5 (br s, 2H, NH_2); 7.43 (t, 1H, $J_{1-2} = J_{2-3}$ = 8.19 Hz, 2-H); 7.56 (t, 1H, $J_{7-8} = J_{8-9}$ = 7.51 Hz, 8-H); 7.64 (t, 1H, 3-H); 7.76 (d, 1H, 4-H); 7.92 (d, 1H, 9-H); 7.98 (br d, 1H, J_{7-8} = 6.14 Hz, 7-H); 9.6 (d, 1H, 1-H). ^{13}C NMR ($CDCl_3$): 121.3 (1a-C); 122.8 (7a-C); 123 (7-C); 123 (2-C); 126.6 (4-C); 127 (8-C); 127.1 (1-C); 129.7 (3-C); 131.3 (10a-C); 132 (10-C); 135.2 (9-C); 144 (4a-C); 154.0 (6-C).
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