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An expedient one-pot synthesis of novel 10-substituted 9-aminophenanthrenes

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ABSTRACT

An efficient synthesis of 9,10-disubstituted phenanthrenes is described in this Letter. These novel useful building blocks were obtained in a one-pot reaction including Suzuki–Miyaura cross-coupling followed by a Dieckmann–Thorpe ring closure under microwave irradiation. The selection of the appropriate reagents and the optimal reaction conditions to isolate the intermediate biphenyl compound or the final substituted phenanthrenes in high yields will be discussed in this Letter.

1. Introduction

Phenanthrene rings are extensively present in natural products,[1] which possess interesting biological activity such as antimalarial[2] or cytotoxic activity.[3] These systems have also been studied and developed for their important properties either in materials science[4] or in medicinal chemistry.[5]

Many routes have been explored toward these useful cycles. Two main routes are usually described to generate the appropriate structure **I** (Fig. 1). The first one deals with the synthesis of a stilbene **II**, suitable for an intramolecular aryl–aryl bond formation (connection B then A). Many mechanisms have been recently explored in that aim including oxidative coupling.[6] The second and reverse route (connection A then B) requests the preparation of substituted biphenyls **III** which were finally submitted to an intramolecular ring closure. If the synthesis of 2,2′-biphenyl **III** has been extensively studied,[7] the development of transition-metal-catalyzed cross-coupling has conducted to huge improvement in their access.[8] This novel methodology has recently allowed highly efficient one-pot synthesis of substituted phenanthrenes.[9]

Despite these recent advances, novel syntheses are needed, especially to create more diversity on the phenanthrene ring system. This is notably the case of 10-substituted 9-aminophenanthrene ring systems which have been rarely described. Most of the examples exposed their access through the reduction of their nitro analog (route 1, Fig. 2).[10]

A second reaction has been used to afford α,β-diphenyl-β-aminoethanol by reduction of the corresponding *o*-quinone monooxime (route 2).[11] A third route introduced an aryl group on position 10 by coupling with an aryllead triacetate (route 3).[12] More recently the synthesis of 10-aryl-9-aminophenanthrenes has been reported by reaction of the anion of 9-aminophenanthrene with aryl halides (route 4).[13] All these syntheses are introducing the diversity from an already prepared phenanthrene ring system. Only two routes described the formation of the amino substituent according to a nitrile cyclization. The acidic ring closure of 2-biphenylylacetonitrile (route 5) leading to novel 10-alkyl-9-aminophenanthrenes was exposed in the first one.[14] More recently during his work concerning Directed *ortho*-Metalation (DoM), Snieckus group has studied the synthesis of various 9-aminophenanthrenes from the corresponding 2-cyano-2′-methyl biaryls.[15] Starting from 9-phenanthrols a 10-methoxy 9-aminophenanthrene (route 6) was synthesized in two steps using lithium diethyl amide as a base.

Considering the experience of our laboratory in the synthesis of functionalized heterocycles,[16] we have designed a two-step synthesis (route 7) of novel 10-substituted-9-aminophenanthrenes. During the preparation of this work, a paper has described a similar strategy[9b] that however has never been exploited toward the synthesis of aminophenanthrene. Moreover, our strategy will offer the opportunity to access novel *o*-aminoesters of phenanthrene, which could be used as a very useful building block according to the great reactivity of anthranilic acid.[17]

In our approach, a Suzuki–Miyaura cross-coupling between partner **1** and *o*-cyanoboronic ester **2** will first form the appropriate biphenyl compound (route 6). The second step will be to realize

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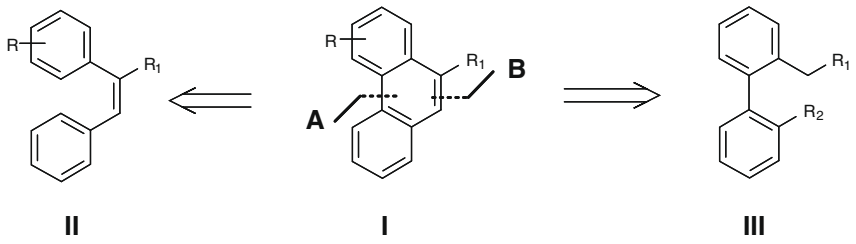


Figure 1. Main routes toward 9-substituted phenanthrenes.

a nitrile cyclization again but with the anion of an activated methylene present on the second aryl group according to a Dieckmann–Thorpe mechanism. Furthermore, this procedure will introduce on the phenanthrene ring system more diversity with the presence for the first time of an electron-withdrawing group in position 10.

2. Results and discussion

In order to verify the validity of our strategy, the two steps were evaluated individually. The requested boronic ester **2** was obtained from an *ortho*-lithiation of benzonitrile (Scheme 1).[18] The latter was involved in a Suzuki–Miyaura reaction with methyl 2(2-bromophenyl)acetate **1a** under microwave irradiation to afford in good yield and in 5 min the expected biphenyl **3a**.[19] The reaction has been run under standard conditions in dioxane using $Pd(PPh_3)_4$ as a catalyst and cesium carbonate as a base. Biphenyl **3a** was then submitted to a Dieckmann–Thorpe ring closure in methanol using potassium carbonate as a base to afford, after 20 min under microwave irradiation, the expected aminoester **4a** in 85% yield.[20]

Having demonstrated the feasibility and the efficiency of our strategy, we then decided to optimize it in a one-pot cascade reaction. Our first attempt was to add one more equivalent of base in the Suzuki reaction and to increase the reaction time (entry 1 in Table 1). Unfortunately, if the expected phenanthrene **4a** was isolated, the yield remains very low and the corresponding biphenyl compound **3a** would remain as the major product. Dieckmann–Thorpe ring closures are usually realized in protic solvent. Addition of MeOH in the reaction mixture did not improve the reaction (entry 2 in Table 1). The use of toluene in place of dioxane did not make any difference (entry 3).

However, a one-pot two-step method brought many improvements. After 5 min under classical Suzuki conditions, 200 μL of MeOH was added to the closed reactor and the heating was prolonged for 20 min (entry 4). For the first time these conditions led to the expected phenanthrene **4a** with good conversion and in high yield. Addition of EtOH instead of MeOH led to the same reactivity but to a side transesterification reaction. These results were encouraging and proved the great influence of protic solvent on the final ring closing reaction.

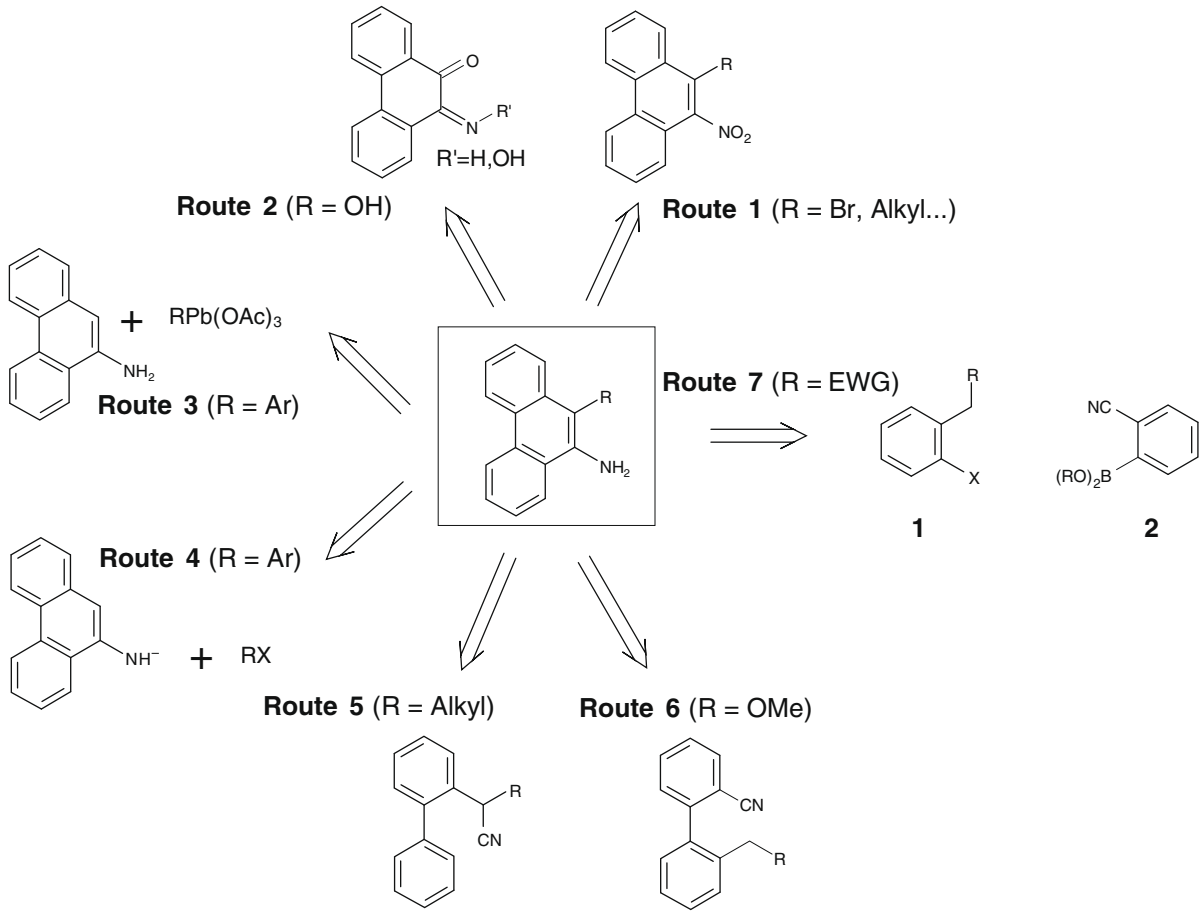
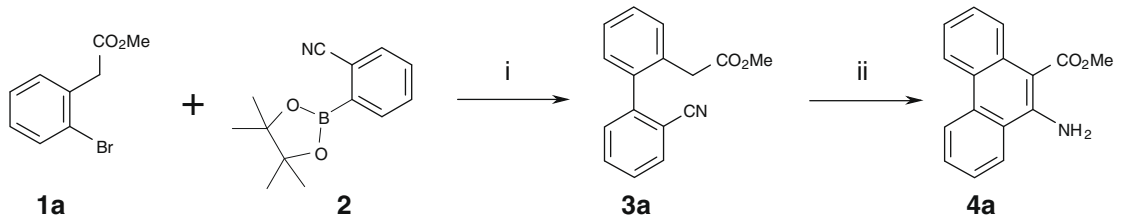
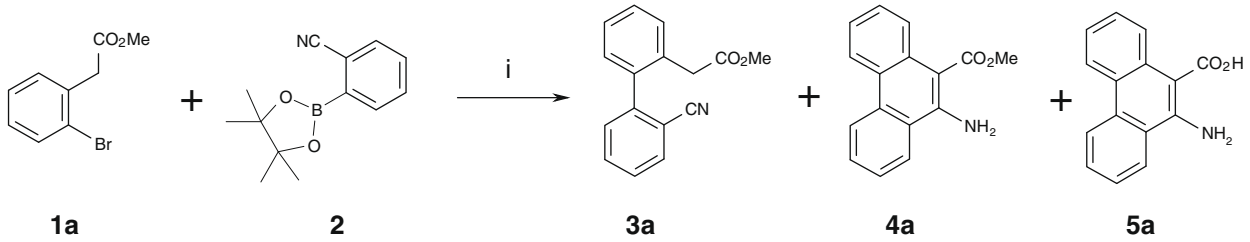


Figure 2. Principal synthesis of 10-substituted 9-aminophenanthrenes.



Scheme 1. Reagents and conditions: (i) $Pd(PPh_3)_4$ 5%, Cs_2CO_3 2 equiv, dioxane, MW 120 °C, 5 min, 90% yield; and (ii) MeOH, K_2CO_3, MW 20 min, 85%.

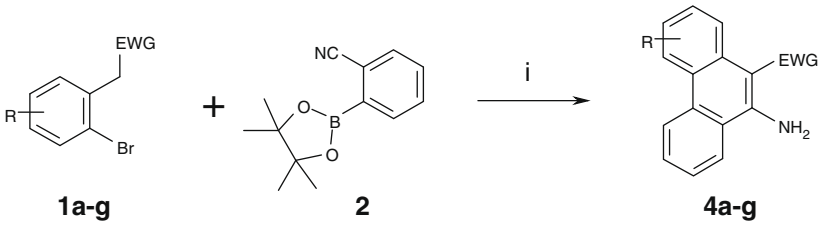


Scheme 2. Reagents and conditions: (i) **1a** 0.01 mol, Pd cat, 5%, **2** 1.1 equiv, base 3 equiv, solvent 2 mL, MW. See Table 1 for details.

Table 1
Derivative **4a** produced via Scheme 2

Entry	Pd	Base	Solvent	Time (min)	*T* (°C)	Yield (%)		
						3a	**4a**	**5a**
1	$Pd(PPh_3)_4$	Cs_2CO_3	Dioxane	50	120	80	5	
2	$Pd(PPh_3)_4$	Cs_2CO_3	Dioxane/MeOH[a]	50	120	86	14	
3	$Pd(PPh_3)_4$	Cs_2CO_3	Toluene/MeOH[a]	50	120	90	10	
4	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**Dioxane then MeOH[a]**	**25**	**120**	**2**	**80**	
5	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	50	120	45	35	
6	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**DMF**	**20**	**150**	**0**	**85**	
7	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	20	200	9	0	60
8	$Pd(OAc)_2$	Cs_2CO_3	DMF	50	120	0	0	
9	$Pd(PPh_3)_4$	*t*-BuOK	DMF	20	150	0	0	
10	$Pd(PPh_3)_4$	K_3PO_4	DMF	20	150	84	16	

[a] Toluene/MeOH 10/1.



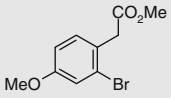
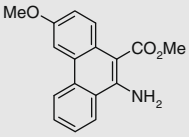
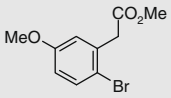
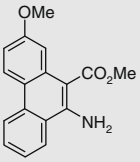
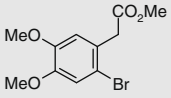
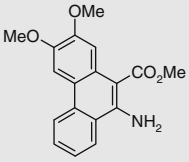
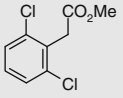
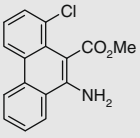
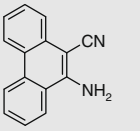
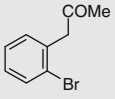
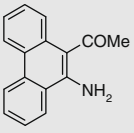
Scheme 3. Reagents and conditions: (i) **1a–g** 0.01 mol, $Pd(PPh_3)_4$ cat, 5%, **2** 1.1 equiv, Cs_2CO_3 3 equiv, DMF 2 mL, MW.

Table 2
Derivative **4a** produced via Scheme 2

Entry	Pd	Base	Heating	Solvent	Time (min)	*T* (°C)	Yield (%)		
							3a	**4a**	**5a**
1	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**Microwave**	**DMF**	**25**	**150**	**0**	**85**	
2	$Pd(PPh_3)_4$	Cs_2CO_3	Oil bath, sealed tube	DMF	120	150	45	35	
3	$Pd(PPh_3)_4$	Cs_2CO_3	Oil bath, sealed tube	DMF	240	150	25	35	25
4	$Pd(PPh_3)_4$	Cs_2CO_3	Oil bath, round-bottomed flask	DMF	24 h	150	15	0	

DMF was then used (entry 5) and led after 50 min at 120 °C to **4a** in 35% yield. If the temperature was increased to 150 °C, **4a** was obtained as the major product after 20 min in 85% yield (entry 6). These conditions appear to be the best to achieve both the coupling and the ring closure in that series.[21] Indeed heating the reaction mixture to 200 °C led this time to the saponified ester **5a**

Table 3
9-Aminophenanthrene derivatives **4a**–**g** produced via Scheme 3

Entry	Starting material		Product		Time (min)	Yield (%)
1		**1b**		**4b**	45	75
2		**1c**		**4c**	50	72
3		**1d**		**4d**	20	76
4		**1e**		**4e**	20	80
5		**1f**		**4f**	20	85
6		**1g**		**4g**	20	88

(entry 7). We then decided to explore the influence of the catalyst or the base (entry 8–10), with the evidence of better conditions when $Pd(PPh_3)_4$ and Cs_2CO_3 were used.

Following this study we have also explored the nature and the influence of the thermal activation (Table 2). After 2 h at 150 °C in an oil bath and in a sealed tube most of the starting material has been converted, but only 35% of **4a** was obtained. Extension of the reaction time mostly produced the saponified compound **5a** (entry 3 in Table 2). Pressure conditions appear to be relevant in our case. If the reaction is run in a round-bottomed flask, only a small trace of the biphenyl **3a** is isolated after 24 h.

In order to widen the scope of our reaction, various substituted *ortho*-bromophenylacetates were first introduced in our optimized one-pot procedure. For two compounds, **1b** and **1c**, the presence of the methoxy group induced longer reaction time in order to reach total consumption of the starting material (entries 3 and 4 in Table 3). Good results were also obtained from the dimethoxy analog **1d** (entry 3). The good yield obtained from dichlorophenylacetate **1e** proved that the bromine atom could be easily replaced by a chlorine atom in the Suzuki–Miyaura cross-coupling reaction (entry 4).

We have decided to study the replacement of the electron-withdrawing group. If particular care is needed to control the reaction with the ester group (**4a–4e**), the reaction appears to be really efficient to easily obtain amino nitrile phenanthrene **4f**. Indeed this compound was isolated in an efficient one-pot procedure and 85% yield, compared to the longer previously described sequence.[10] Very good yields were also obtained starting from another activated methylene compound, 1-(2-bromophenyl)propan-2-one **1g** (entry 6).

3. Conclusion

In conclusion, we have demonstrated that our one-pot sequence could be an efficient method to synthesize highly functionalized aminophenanthrenes. This synthesis, consisting of a Suzuki cross-coupling and a subsequent Dieckmann–Thorpe cyclization, appears to be a fast and effective method to access interesting phenanthrene building blocks. The use of the latter and the application of this methodology to various novel heterocycles will be reported in due time.

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19. *General procedure for the Suzuki–Miyaura cross-coupling*: Synthesis of **3a**. To a solution of aryl bromide **1a** (100 mg, 0.37 mmol) in 2 mL dioxane were added cyanoboronic ester **2** (95 mg, 0.41 mmol), $Pd(PPh_3)_4$ (14 mg, 5%), and Cs_2CO_3 (241 mg, 0.74 mmol). The mixture was irradiated at 120 °C for 5 min using a microwave reactor. The reaction mixture was then diluted with EtOAc, filtrated on a small pad of Celite, and concentrated under vacuum. The crude mixture was then purified by column chromatography (DCM/CyHex 7/3) to afford an orange oil in 90% yield. IR (KBr) 2951, 2225 (CN), 1732 (CO), 1434, 1247, 1211, 1007, 759, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 4.04 (s, OCH_3), 3.44 (dd, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.53, 144.67, 138.38, 132.93, 132.39, 132.04, 130.72, 130.67, 130.00, 129.10, 127.96, 127.46, 117.84, 113.01, 52.02, 38.78. HRMS (EI) calcd for $C_{16}H_{13}NO_2$ 251.09461, found 251.09554.
20. *General procedure for the ring closure*. Synthesis of **4a**. (a) To a solution of **3a** (100 mg, 0.40 mmol) in 2 mL MeOH was added K_2CO_3 (55 mg, 0.44 mmol) and the reaction mixture was irradiated at 120 °C using a microwave reactor before concentrating under vacuum. The crude mixture was then purified by column chromatography (DCM/CyHex 7/3) to afford an orange solid in 85% yield. Mp: 69 °C; IR (KBr) 3459, 3352 (NH_2), 2944, 1672 (CO), 1597, 1431, 1302, 1225, 1149, 1092, 742, 730, 717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.0 Hz,1H), 8.51 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.30 (s, 2H, NH_2), 4.04 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.38(CO), 144.56, 131.57, 129.58, 127.90, 126.26, 125.75, 124.52, 124.25, 123.13, 122.43, 122.27, 121.51, 120.88, 101.75, 50.69. HRMS (EI) calcd for $C_{16}H_{13}NO_2$ 251.09461, found 251.09501.
21. *General one-pot procedure*. To a solution of aryl bromide **1** (0.37 mmol) in 2 mL dioxane were added cyanoboronic ester **2** (0.41 mmol), $Pd(PPh_3)_4$ (5%), and Cs_2CO_3 (1.11 mmol). The mixture was irradiated at 150 °C for 20 to 50 min using a microwave reactor. The reaction mixture was then diluted with EtOAc, filtrated on a small pad of Celite, and concentrated under vacuum. The crude mixture was then purified by column chromatography (DCM/CyHex 7/3) to afford the corresponding phenanthrene.