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A novel approach to phenanthro[9,10-*d*]pyrimidines *via* an intramolecular Stille-type biaryl coupling reaction

Roberto Olivera, Sergio Pascual, Maite Herrero, Raul SanMartin, Esther Domínguez*

Kimika Organikoa Saila, Zientzi Fakultatea, Euskal Herriko Unibertsitatea, P.O.Box 644 - 48080 Bilbao. Basque Country (Spain)

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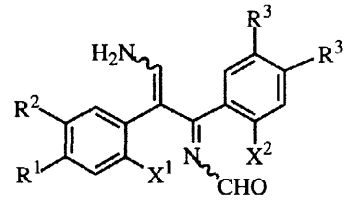
Abstract: New 4,5-*o,o*-dihaloarylpyrimidines, readily obtained from the corresponding enaminoketones, are transformed into phenanthro[9,10-*d*]pyrimidines by means of a high-yielding tandem stannylation/biaryl coupling procedure. Proof of the pyrimidine formation mechanism is also presented.

Keywords: coupling reactions; policyclic heterocyclic compounds; pyrimidines

Phenanthrene derivatives are good DNA-chain intercalators mainly due to their planarity. Likewise, applications as both antineoplastic and mutagen agents have been described.[1] Phenanthro[9,10-*d*]fused heterocycles have been reported to present very interesting pharmacological properties.[2] This framework also constitutes the core of several natural products such as cryptopleurine, thyloforine, and antofine.[3]

Our recent advances in the synthesis of diaryl substituted isoxazoles and pyrimidines[4] encouraged us to attempt a new approach to the above mentioned phenanthro[9,10-*d*]heterocyclic systems *via* biaryl coupling reactions, since other existing methodologies (photocyclization of *cis*-stilbenes,[5] cyclization of thioketone and 4-alkoxyphenylethinyl derivatives,[6] annelation reaction between alkynes and iodobiaryls,[7] and heterocyclization of phenanthrene derivatives[8]) usually fail on performing large-scale reactions or present serious limitations concerning substitution patterns in the precursor.[5-8,9]

As shown in Scheme 1, enaminoketones **1**, readily prepared from the corresponding diaryl ketones,[10] were submitted to Leuckart reductive amination conditions following known procedures,[4b] affording 4,5-*o,o*-dihaloarylpyrimidines **2**[11] with good yields. With regard to the heterocycle formation process, intermediate **3**[12] was isolated as a mixture of diastereoisomers, providing additional proof of the amine-exchange based mechanism recently proposed.[4b]



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Our attention was then focused on the biaryl coupling needed to obtain the target tetracycle. The preparation of arylboronic acids or aryltrialkylstannanes, by reaction of the corresponding organolithium derivative and trimethyl/triisopropylborate (Suzuki-Miyaura reaction)[13] or trimethyl/tributyltin chloride (Stille methodology)[14] respectively, failed probably due to a lack of control at the metal-halogen exchange, as has been recently reported for some dihalogenated substrates.[15] Nevertheless, one-pot aryltrimethylstannane formation/coupling reaction to afford phenanthro[9,10-*d*]pyrimidines **4**[16] was achieved with great success

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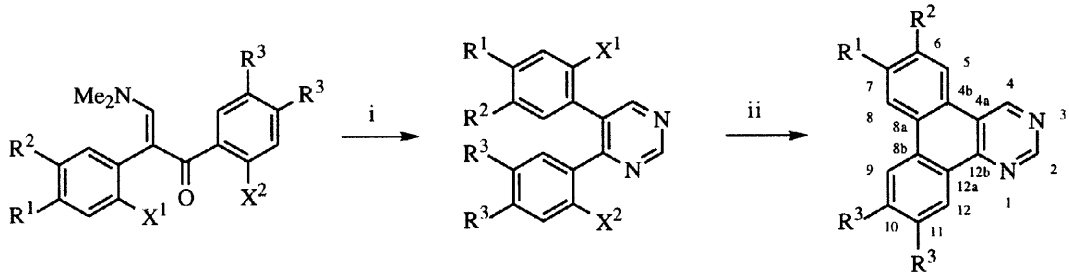
(85-91%) when pyrimidines **2** were reacted with Me_6Sn_2 as the organometallic reagent[17] and $Pd(PPh_3)_4$ or $Pd(PPh_3)_4Cl_2$ as the catalyst[18] (3-8%) in dioxane solution at 140°C.[19] The reaction was performed in a heavy-wall pressure tube, as only dehalogenation products were isolated when refluxing both diiodinated and dibrominated substrates along with the reagents.



1 **2** **4**

i: $NH_4^+HCOO^-$, $HCONH_2$, HCOOH, 150-165°C
ii: Me_6Sn_2, $Pd(PPh_3)_4$, dioxane, pressure tube, 140°C

Scheme 1.

Table 1. 4,5-*o,o*-Dihaloarylpyrimidines **2** and phenanthro[9,10-*d*]pyrimidines **4**.

R^1	R^2	R^3	X^1	X^2	**2** (%)[a]	m.p. (°C)[b]	**4** (%)[a]	m.p. (°C)
H	H	H	Br	Br	**a** (71)	144-146	**a** (89)	170-172[c]
H	H	H	I	I	**b** (81)	160-162	**a** (91)	"
OMe	OMe	OMe	Br	Br	**c** (76)	134-135	**b** (85)	236-238[d]
OMe	OMe	OMe	I	I	**d** (68)	149-151	**b** (80)	"
H	H	OMe	Br	Br	**e** (73)	65-67	**c** (79)	234-236[d]
H	H	OMe	I	I	**f** (66)	80-82	**c** (83)	"
OMe	OMe	H	Br	Br	**g** (79)	105-106	**d** (77)	215-216[c]
OMe	OMe	H	I	I	**h** (61)	148-149	**d** (81)	"
OMe	OMe	H	Br	I	**i** (66)	114-115	**d** (61)	"
OMe	OMe	H	I	Br	**j** (76)	134-136	**d** (66)	"
OCH_2O		H	I	Br	**k** (66)	159-160	**e** (86)	240-241[c]

[a] Yield of pure crystallized compound; [b] Crystallized from methanol;
[c] Crystallized from hexane/ethyl acetate, 6:4; [d] Crystallized from diethyl ether

It should be pointed out that the target coupling products were obtained with quite similar yields from both diiodo and dibromo precursors, or even mixed iodobromo derivatives, so a significant advantage of our method is that bromo derivatives, which are usually cheaper and easier to prepare, may be used as suitable substrates. Moreover, no significant change was observed when employing electron-donating OMe substituted derivatives, which are generally accepted to undergo a slower transmetallation step.[20]

Finally, regarding coupling reaction results, it may be proposed that the extended degree of conjugation of the final tetracyclic product probably compensates for the steric constraint[21] at the transmetallation step of such a Stille-type process.[22]

To sum up, considering that very few examples of such an intramolecular coupling reaction *via* tandem or domino processes have been reported to date,[23] we can conclude that not only does the synthetic path presented above constitute an efficient approach to the phenanthro[9,10-*d*]pyrimidine framework, but also a meaningful example of intramolecular biaryl coupling in a quite sterically constrained molecule.

At present, we are trying to extend the scope of this approach to other similar tetracyclic systems incorporating different heterocyclic cores.

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11. Selected data for representative 4,5-diarylpyrimidine **2a**: R_f (hexane/EtOAc, 55:45) 0.5; FT-IR (film) cm^{-1}: 3052, 1592, 1560; ^1H NMR (250 MHz, $CDCl_3$): δ 7.11-7.24 (6H, m, H_{arom}), 7.53-7.61 (2H, m, H_{arom}), 8.82 (1H, s, H-6), 9.35 (1Hs, s, H-2); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 121.8, 123.4 (C_{arom}-C, C_{arom}-Br), 127.0, 127.2, 130.0, 130.2, 131.4, 133.6 (Carom-H), 133.7, 135.6, (C_{arom}-C, C_{arom}-Br), 138.2 (C-5), 157.5 (C-6), 158.9 (C-2), 164.2 (C-4); EI-MS: *m/z* 392 (M+2, 17), 390 (M^+, 32), 388 (M-2, 18), 311 (47), 319 (47), 230 (100), 176 (22).

12. The diaryl formyliminoenamine framework was assigned to intermediates **3k** (R^1=R^2= OCH_2O R^3= H; X^1= I, X^2= Br) and **3f** (R^1=R^2=H, R^3= OMe; X^1=X^2= I) basing on the following spectroscopic data of the corresponding diastereomeric mixtures: FT-IR (film) cm^{-1}: 3270-3460 (ν_{N-H}), 1710 ($\nu_{C=O}$), 1620-1615 ($\nu_{C=O}$), 1570 ($\nu_{C=C}$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.78-8.19 (1H, s, H-CO), 6.70-7.45 (H_{arom}, =CH); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 140.5-141.6 (=CH-N), 158.4-162.0 (CO); EI-

MS **a**: *m/z* 427 (M+2-CHO, 3), 427 (M-CHO, 6), 427 (M-2-CHO, 4), 374.1 (M-Br, 14), 372.1 (M-Br, 14), 346 (M-Br-CHO, 77), 344 (M-Br-CHO, 77), 264 (M-2Br-CHO, 100); **b**: *m/z* 534 ((M-CHO, 4), 408 (M-I-CHO, 17), 280 (M-2I-CHO, 100)

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16. Selected data for representative phenanthro[9,10-*d*]pyrimidine **4a**: R_f (hexane/EtOAc, 55:45) 0.4; FT-IR (film) cm^{-1}: 3049, 2955, 2920, 1678, 1609, 1570; ^1H NMR (250 MHz, $CDCl_3$): δ 7.69-7.84 (4H, m, H_{arom}), 8.51-8.58 (3H, m, H_{arom}), 9.21 (1H, dd, *J* =7.9Hz, *J* =1.5Hz, H-5), 9.42 (1H, s, H-2), 10.0 (1H, s, H-4); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 121.6 (C_{arom}-C), 122.3, 122.6, 123.4, 125.5 (Carom-H), 126.5 (C_{arom}-C), 127.7, 127.9, 128.6 (Carom-H), 129.3 (C_{arom}-C), 130.8 (Carom-H), 133.0 (C_{arom}-C), 151.0 (C-12b), 153.3, 156.0 (C-2, C-4); EI-MS: *m/z* 230 (M^+, 100), 229 (16), 176 (28), 88 (21).

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19. Typical procedure: *Phenanthro[9,10-d]pyrimidine* **4a**. A heavy wall-pressure tube was charged with diarylpyrimidine **2a** (53 mg, 0.136 mmol), $Pd(Ph_3P)_4$ (7.9 mg, 6.8 μmol), and degassed dioxane (4.2 ml) under nitrogen. A solution of Sn_2Me_6 (49 mg, 0.15 mmol) in degassed dioxane (1.5 ml) was added to the resulting suspension, and after flushing with nitrogen at room temperature for 15 min., the mixture was heated at 150°C in an autoclave for 22 h. After cooling, the resulting black suspension was centrifuged and the corresponding solution was evaporated *in vacuo*. The residue was purified by flash-chromatography (SiO_2, hexane/EtOAc 8:2 as solvent) to afford phenanthro[9,10-*d*]pyrimidine **4a** (25 mg, 89%) as a yellow powder.

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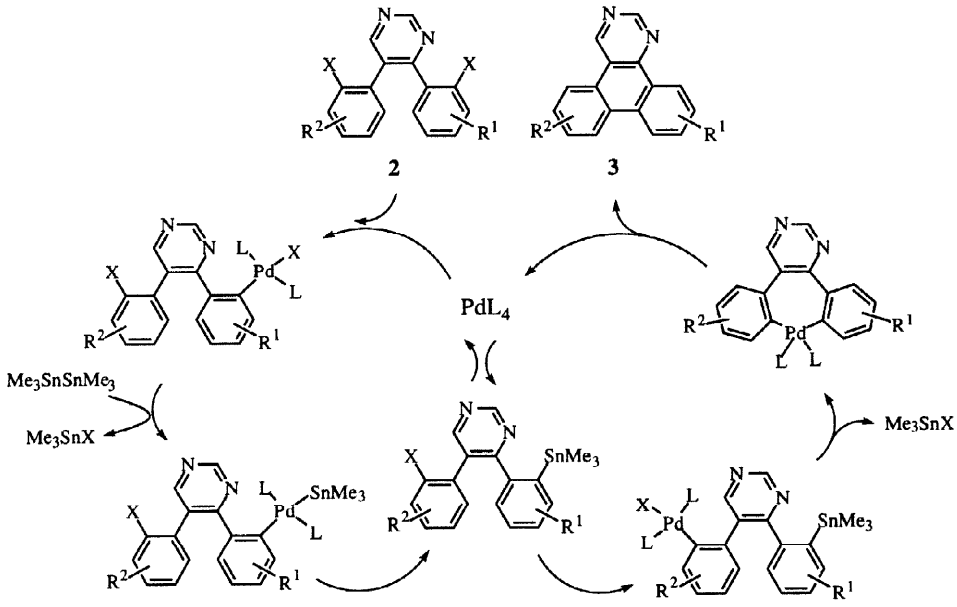
22. A proposal for the mechanism based on previous reports regarding Stille coupling reactions (Farina, V.; Krishnan, B. *J. Am. Chem. Soc.*, **1991**,*113*, 9585) is shown below:



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