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Phenyliodine(III) *bis*(trifluoroacetate) mediated synthesis of phenanthro[9,10-*d*] fused isoxazoles and pyrimidines

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Abstract: A novel protocol for the PIFA mediated regioselective oxidative coupling of 4,5-diaryl substituted isoxazoles and pyrimidines leading to new phenanthro[9,10-*d*]heterocyclic systems is reported. © 1999 Elsevier Science Ltd. All rights reserved.

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An important enzyme-catalyzed oxidation step in which two phenol derivatives become coupled to yield a biaryl moiety often occurs in the course of the biosynthesis of many natural products.[1] Such oxidative coupling reactions, formerly developed for phenols[2] and later extended to phenol ethers and other oxygenated, electron-rich arenes,[3] are effected by anodic oxidation[4] and several oxidants,[3,5] mostly heavy metal reagents.[6] In comparison with a photochemical approach, oxidative coupling is reported to show no serious limitations concerning substitution patterns in the substrate,[7] and as no halogenated precursors are required, oxidative coupling constitutes in many cases a valid alternative to Ullmann, Suzuki, or Stille biaryl coupling methodologies.[8] A straightforward synthesis of phenanthro[9,10-*d*]pyrimidines **2** has recently been reported by our group, in which an intramolecular Stille-type biaryl coupling reaction of 4,5-*o*,*o*-dihaloarylpyrimidines of type **4**[9] was the key step. Considering all this, the aim of the present research is to describe a new, simple and practical one-pot protocol for the regioselective synthesis of the phenanthro[9,10-*d*]heterocyclic framework, which constitutes the core of several natural products and pharmacologically interesting compounds.[10]

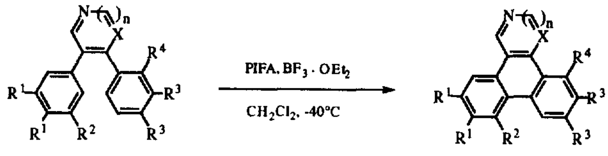
As shown in Table 1, 4,5-bis-(3,4-dimethoxyphenyl)isoxazole **3a**[11a] was submitted to the action of oxidizing agents containing Fe(III), I(III), Tl(III), Ru(IV) and V(V)[12] in order to promote an oxidative coupling to give 5,6,9,10-tetramethoxyphenanthro[9,10-*d*]isoxazole **1a**. Both $FeCl_3$ and PIFA (phenyliodine(III) bis(trifluoroacetate) provided good yields of the target phenanthro derivative **1a** (Table 1, entries 7 and 8) but the use of $FeCl_3$ was discarded due to the difficulties which arose on removing metallic byproducts during the work-up and further purification, as could be confirmed by a marked distortion of the NMR signals.

Table 1. Summary of the oxidative coupling assays leading to phenanthroisoxazole **1a**

Entry	Reaction conditions	Reaction time (h)	Ref.	1a (%)
1	TTFA[a] (1.1 eq.), CH_2Cl_2, r.t	6.5	12a	42
2	TTFA[a] (1.1 eq.), TFAA,[b] TFA,[c] $BF_3 \cdot OEt_2$, 0°C	4	12b	67
3	TTFA[a] (1.1 eq.), CH_3CN, CCl_4, $BF_3 \cdot OEt_2$, 40°C→ 0°C	75	12c	72
4	$RuO_2 \cdot 2\,H_2O$ (4 eq.), TFAA,[b] TFA,[c] $BF_3 \cdot OEt_2$, CH_2Cl_2, -10°C→ r.t	7	12d	71
5	VOF_3 (3.3 eq.), $BF_3 \cdot OEt_2$, CH_2Cl_2, r.t	0.15	12e	49
6	VOF_3 (3 eq.), TFA,[c] CH_2Cl_2, -45°C→ r.t	6	12f	69
7	$FeCl_3$ (6 eq.), CH_2Cl_2, r.t	6.7	12g	80
8	PIFA (1.1 eq.),[d] $BF_3 \cdot OEt_2$, CH_2Cl_2, -40°C	0.25	12h	85

[a] TTFA: $Tl(OCOCF_3)_3$; [b] TFAA: $(CF_3CO)_2O$; [c] TFA: CF_3COOH; [d] PIFA: $PhI(OCOCF_3)_2$

PIFA has received much attention[13] as a convenient oxidant which avoids the formation of electrophilic aromatic metallation side-products.[12a] Taking into account the excellent yield obtained for phenanthroisoxazole **1a**, diarylisoxazoles **3b-d** and pyrimidines[11b] **4a-e** were submitted to PIFA oxidation conditions,[14] providing the corresponding phenanthro derivatives **1** and **2** respectively, with the results summarized in Table 2.



n=0, X=O **3**
n=1, X=N **4**

n=0, X=O **1**
n=1, X=N **2**

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Table 2. Phenanthro[9,10-*d*]isoxazoles **1** and phenanthro[9,10-*d*]pyrimidines **2** prepared.

Entry	Substrate	R^1	R^2	R^3	R^4	Product (%)[a]	m.p. (°C)
1	**3a**	OMe	H	OMe	H	**1a** (85)	216-217[b]
2	**3b**	H	H	H	H	-	-
3	**3c**	H	H	OMe	H	**1c** (80)	188-189[c]
4	**3c**	OMe	H	OMe	OMe	**1d** (61)	189-190[c]
5	**4a**	OMe	H	OMe	H	**2a** (74)	236-238[c]
6	**4b**	H	H	H	H	**2b** (23)	170-172[b]
7	**4c**	H	H	OMe	H	**2c** (81)	234-236[d]
8	**4d**	OMe	H	OMe	OMe	**2d** (51)	238-239[c]
9	**4e**	OMe	OMe	OMe	H	**2e** (88)	228-229[c]

[a] Yield of pure crystallized compound; [b] Crystallized from hexane/ethyl acetate (1:1)
[c] Crystallized from methanol; [d] Crystallized from diethyl ether

It should be pointed out that diaryl heterocycles 3 and 4 reacted regioselectively,[16] as no regioisomer of any of the corresponding phenanthro derivatives 1 and 2 was detected. Comparing the results obtained from precursors **3b** and **4b** (Table 2, entries 2 and 6), it can be proposed that, when both aryl substituents were phenyl groups, a pyrimidine heterocycle, unlike isoxazole, could promote a slight stabilization of the aromatic radical cation intermediate which would lead to a low-yielding but meaningful coupling reaction. Finally, in spite of the lack of activation in one of the aryl rings (phenyl)[12a,12f] of the substrate, our methodology provides the corresponding tetracyclic products **1c** and **2c** (Table 2, entries 3 and 7) with excellent yields.

In summary, a full study of different oxidizing agents for the non-phenolic intramolecular oxidative coupling of 4,5-diarylisoxazoles and 4,5-diarylpyrimidines has led us to a simple and efficient synthetic approach to the phenanthro[9,10-*d*]heterocyclic system, effected by the convenient hypervalent iodine reagent PIFA. In addition, significant examples of coupling reactions, with the participation of non-activated arenes, and a possible pyrimidine induced activation to explain the coupling observed between two phenyl moieties, are also reported. Further experiments in order to expand the scope of this procedure to other heterocyclic systems are now in progress.

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14. Typical procedure: 5,6,9,10,11-*pentamethoxyphenanthro*[9,10-*d*]*isoxazole* **1d**. A solution of PIFA (0.31 mmol) in dry dichloromethane (1 cm^3) was added to a stirred solution of diarylisoxazole **3d** (0.28 mmol) in dry dichloromethane (4 cm^3) at -40°C under argon. After adding boron trifluoride diethyl etherate (0.32 mmol), the resulting brown solution was stirred for 15 min. at -40°C, allowed to warm at room temperature and absorbed on silica gel (725 mg). Purification by flash-chromatography (silica gel, 50% hexane/ethyl acetate as eluent) provided phenanthroisoxazole **1d** as a yellow powder (63 mg, 61%).
15. Selected data for representative phenanthro[9,10-*d*]isoxazole **1d** : δ_H (250 MHz, $CDCl_3$) 4.06 (3H, s, OMe), 4.11 (3H, s, OMe), 4.12 (3H, s, OMe), 4.14 (3H, s, OMe), 4.19 (3H, s, OMe), 7.43 (1H, s, H-4), 7.67 (1H, s, H_{arom}), 7.81 (1H, s, H_{arom}), 9.03 (1H, s, H-3); δ_C (62.8 MHz, $CDCl_3$)56.1, 56.2, 61.4, 62.0 (OMe), 100.5, 104.4, 105.0 (C_{arom}-H), 110.0, 113.8, 120.1, 128.4 (C_{arom}-C), 144.5 (C-3), 142.0, 148.5, 149.2, 150.2, 154.5 (C_{arom}-O), 159.0 (C-11b); EI-MS: *m/z* 369 (M^+, 100), 354 (19), 311 (26), 296 (10), 268 (10), 240 (17).
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