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Synthesis of 6-Phenanthridinones and Their Heterocyclic Analogues through Palladium-Catalyzed Sequential Aryl–Aryl and *N*-Aryl Coupling

Raffaella Ferraccioli,*,† Davide Carenzi,† Ottavio Rombolà,‡ and Marta Catellani*,‡

CNR−Istituto di Scienze e Tecnologie Molecolari (ISTM), Dipartimento di Chimica Organica e Industriale, Università di Milano, Via C. Golgi 19, 20133 Milano, Italy, and Dipartimento di Chimica Organica e Industriale, Università di Parma, Parco Area delle Scienze, 17/A, 43100 Parma, Italy

raffaella.ferraccioli@istm.cnr.it; marta.catellani@unipr.it

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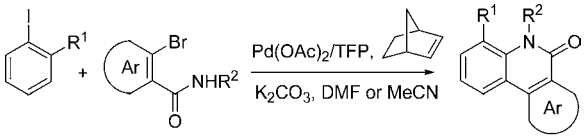
ABSTRACT



Ar: aryl, heteroaryl

yields: 48-90%

6-Phenanthridinones and their heterocyclic analogues were synthesized through a one-pot procedure based on consecutive Pd-catalyzed aryl–aryl and *N*-aryl coupling from iodoarenes ortho-substituted by electron-releasing substituents and amides of *o*-bromoarene- and heteroarenecarboxylic acids.

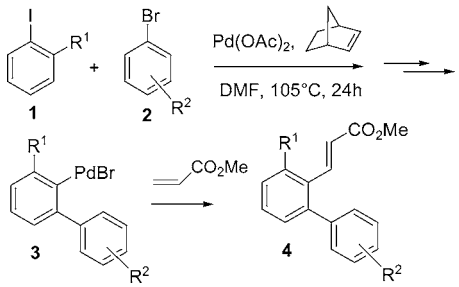
We have recently reported a palladium-catalyzed one-pot sequential reaction involving the aryl coupling of iodoarene **1**, ortho-substituted by an electron-releasing group with bromoarene **2**, bearing an electron-withdrawing substituent. The process is terminated by a Heck reaction (Scheme 1).[1]

In this paper, we further investigate the palladacycle-catalyzed unsymmetrical aryl coupling reaction to obtain nitrogen heterocycles in a one-pot sequence. To this purpose, we wondered whether a suitable functional group such as CONHR in the ortho position of the initial bromoarene **2** could undergo a different termination type intramolecularly at the level of the intermediate **3**, leading to 6-phenanthridinones and their heterocyclic analogues **6** (Scheme 2, R^1 = Me, Et, *i*Pr, MeO; R^2 = H, Me, Bn; Ar: aryl or heteroaryl).

However, our attempts to obtain **6a** from the reaction of **1** (R^1 = Me) and **5a** (R^2 = H) under the previously reported conditions, $Pd(OAc)_2$ as a catalyst, K_2CO_3 as a base, norbornene in DMF at 105 °C,[1] were unsuccessful (Table 1, entry 1) due to the interference of the amide group with palladium.

This failure led us to make the hypothesis that suitable tertiary phosphines could counteract the coordinating action of the amide. We thus investigated the use of tertiary arylphosphines as ligands for $Pd(OAc)_2$ and $Pd_2(dba)_3CHCl_3$

Scheme 1



† CNR-Istituto di Scienze e Tecnologie Molecolari.
‡ Università di Parma.

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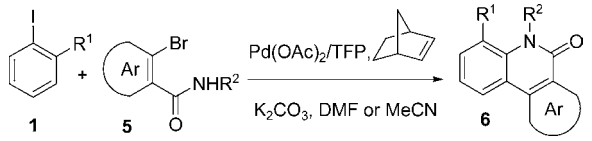
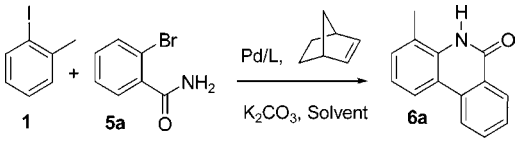
Scheme 2



in DMF and acetonitrile as a solvent. As shown in Table 1, while TPP and P(*o*-tol)$_3$ gave only modest yields of **6a**, good results were obtained with tri-2-furylphosphine (TFP) (entries 3 and 4). The latter was successfully employed by Lautens for the ortho alkylation of palladacycles[2] and by Buchwald in Pd-catalyzed intramolecular arylation of amides.[3]

Table 1. Reaction of **1** (R^1 = Me) and **5a** (R^2 = H) in the Presence of K_2CO_3, Norbornene, Palladium Catalyst, and Ligand in DMF or MeCN[a]

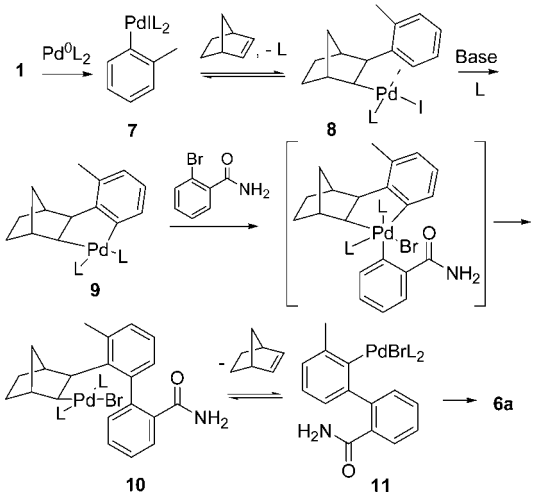


entry	catalyst	ligand	solvent, T (°C)	**6a** (%)[b]
1	$Pd(OAc)_2$		DMF, 105	traces
2	$Pd(OAc)_2$	TFP	DMF, 85	46
3	$Pd(OAc)_2$	TFP	DMF, 105	86
4	$Pd(OAc)_2$	TFP	MeCN, 85	80
5	$Pd(OAc)_2$	TPP	DMF, 105	33
6	$Pd(OAc)_2$	TPP	MeCN, 85	42
7	$Pd(OAc)_2$	P(*o*-tol)$_3$	DMF, 105	c
8	$Pd(OAc)_2$	P(*o*-tol)$_3$	MeCN, 85	10[d]
9	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	MeCN, 85	74
10	$Pd_2(dba)_3{\cdot}CHCl_3$	TPP	MeCN, 85	57
11	$Pd_2(dba)_3{\cdot}CHCl_3$	P(*o*-tol)$_3$	MeCN, 85	19[e]

[a] Reactions of **1** (R^1 = Me, 1 mol equiv) and **5a** (R^2 = H, 1 mol equiv) were run in the presence of norbornene (1.1 mol equiv), K_2CO_3 (2 mol equiv), Pd catalyst (5 mol %), and ligand if present (10 mol %) in DMF or MeCN, 24 h. [**1**] = [**5a**] = 0.045 M. Unless otherwise indicated, conversion of **5a** was complete. [b] Isolated yield. [c] No product **6a** formed; **1** and **5a** were present in a large extent in the crude (^{1}H NMR analysis). [d] Recovery of **5a** = 67%. [e] Recovery of **5a** = 30%.

The reaction proceeds as indicated in Scheme 3 (L = TFP). The *o*-iodotoluene **1** adds to palladium(0), giving complex **7**. Norbornene insertion[4] and subsequent ring closure through C−H activation[5] leads to palladacycle **9**.[6] Bromoamide **5a** then reacts with **9** (probably through oxidative addition leading to palladium(IV) metallacycle, shown in brackets) giving **10**, which results from the attack of the aryl moiety of **5** on the aromatic site of palladacycle **9**. Norbornene

Scheme 3



deinsertion, caused by the steric effect of the two ortho substituents, affords intermediate **11** in which the $CONH_2$ group is in a suitable position to afford an intramolecular amidation[3] of the biphenylylpalladium species leading to **6a**.

This reaction achieves for the first time a consecutive aryl−aryl and *N*-aryl coupling, leading to a phenanthridinone derivative **6a** in a one-pot sequence. In addition, it has been extended to a variety of carboxamides of electron-poor and electron-rich *o*-bromoheterocycles on one side and a variety of iodides ortho-substituted with electron-releasing substituents on the other (Scheme 2, Table 2).

The reactions of **1** (R^1 = Me) with 2-bromobenzamides **5a** (R^2 = H, Me, Bn) proceeded with complete conversion and good yields in DMF and acetonitrile at 105 and 85 °C, respectively (entries 1−4). 3-Bromothiophene-2-carboxamides **5b** (R^2 = Me, Bn) behaved analogously (entries 8−10). On the other side, DMF turned out to be the solvent of choice with the heterocyclic amides **5c**−**f**. For instance, the reaction of 3-bromofurocarboxamide **5c** with **1** (R_1 = Me) in MeCN gave palladium black precipitate and only 32% conversion (entry 12), whereas, in DMF, it gave complete conversion and **6c** was isolated in 82% yield (entry 11). Surprisingly, the reaction with the isomeric 2-bromofuran-3-carboxamide **5d** was less selective leading to **6d** (48% yield) along with a mixture of secondary unidentified

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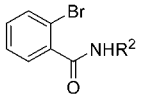
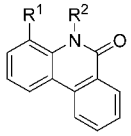
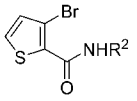
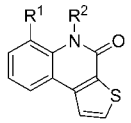
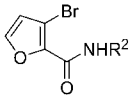
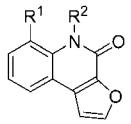
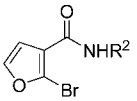
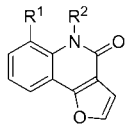
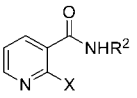
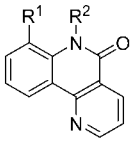
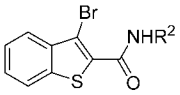
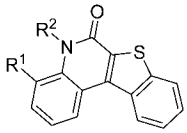
Table 2. Synthesis of **6**[a]

	R^1	**5**	solvent, T(°C)	**6**	yield (%)[b]
					
1	Me	**5a** (R^2 = H)	MeCN, 85	**6a**	80
2	Me	**5a** (R^2 = H)	DMF, 105	**6a**	86
3	Me	**5a** (R^2 = Me)	MeCN, 85	**6a**	87
4	Me	**5a** (R^2 = Bn)	MeCN, 85	**6a**	90
5	Et	**5a** (R^2 = Me)	MeCN, 85	**6a**	75
6	*i*Pr	**5a** (R^2 = Me)	MeCN, 85	**6a**	80
7	OMe	**5a** (R^2 = Me)	MeCN, 85	**6a**	56[c]
					
8	Me	**5b** (R^2 = Me)	MeCN, 85	**6b**	80[d]
9	Me	**5b** (R^2 = Me)	DMF, 105	**6b**	70
10	Me	**5b** (R^2 = Bn)	MeCN, 85	**6b**	78
					
11	Me	**5c** (R^2 = Me)	DMF, 85	**6c**	82
12	Me	**5c** (R^2 = Me)	MeCN, 85	**6c**	24[c]
					
13	Me	**5d** (R^2 = Me)	DMF, 85	**6d**	48
					
14	Me	**5e-Br** (R^2 = Bn)	DMF, 85	**6e**	-[f]
15	Me	**5e-Cl** (R^2 = Me)	DMF, 105	**6e**	55
16	Me	**5e-Cl** (R^2 = Bn)	DMF, 105	**6e**	63
					
17	Me	**5f** (R^2 = Me)	DMF, 50	**6f**	35[g]

[a] Reaction conditions: **1** (1 mol equiv), **5** (1 mol equiv), K_2CO_3 (2 mol equiv), norbornene (1.1 equiv), $Pd(OAc)_2$ (5 mol %), TFP (10 mol %), in MeCN or DMF, 24 h. [**1**] = [**5**] = 0.045 M. Unless otherwise indicated, conversion of **5** was complete. [b] Isolated yield. [c] After 3 h, an extensive palladium black precipitate was formed and the conversion of **5d** was complete. [d] Conversion of **5b** = 97%. [e] Conversion of **5c** = 32%. [f] Crude was a complex mixture in which **5e** was present in very low concentration (^{1}H NMR analysis). [g] $Pd(OAc)_2$ (10 mol %), **1** (2 mol equiv). The reaction proceeded with 60% conversion of **5f**; yield of **6f** was estimated by ^{1}H NMR analysis of an inseparable mixture of **5f** and **6f**, ca. 2:3.

products (entry 13). 2-Bromofuran is reported to be quite reactive in the presence of palladium complexes.[7] As a consequence, 2-bromofuran-3-carboxamide was involved in competitive secondary reactions with loss of selectivity. A similar behavior was observed with *N*-benzyl 2-bromonicotinamide, compound **6e-Br** (R^2 = Bn) being formed in a very small amount (entry 14). Interestingly, in the case of 3-pyridinecarboxamide, selectivity could be enhanced switching from the 2-bromo- to the less reactive 2-chloroderivative.

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Thus, N-substituted 2-chloronicotinamides reacted with **1** giving **6e** (R^2 = Me, Bn) in 55 and 63% yields, respectively (entries 15 and 16). The reaction with 2-bromobenzothiophene-3-carboxamide gave **6f** with 60% conversion of **5f** at 50 °C, in DMF (entry 17). However, we were unable to isolate **6f** as a pure compound, separation from the starting amide being difficult by both chromatography and crystallization. At higher temperature (85 °C), conversion was complete, but selectivity was low.

As previously reported, the presence of ortho electron-donating substituents in the iodoarene **1** is needed to obtain unsymmetrical aryl−aryl coupling.[8] Accordingly, the reaction of **5a** (R^2 = Me) with aryl iodide **1** bearing Et, *i*Pr, or OMe as R^1 led to **6a** in fair to good yields (entries 5−7), final amidation not being affected significantly by the substituent.

6-Phenanthridinones and their heterocyclic analogues are bioactive compounds of current interest as antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, and antiarrhythmic agents, and a number of syntheses have been developed so far to prepare them.[9]

In conclusion, we have developed a new method to obtain 6-phenanthridinones and heterocyclic condensed quinolones **6** based on consecutive palladium-catalyzed regioselective aryl−aryl and *N*-aryl coupling of electron-rich *o*-iodoarenes **1** with *o*-bromobenzamides and/or their heterocyclic analogues **5**. Further investigation of this reaction is currently underway.

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Supporting Information Available: Experimental procedures and characterization for compounds **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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