Intramolecular Palladium-Catalyzed Oxidative Coupling on Thiophene and Furan Rings: Determinant Role of the Electronic Availability of the Heterocycle

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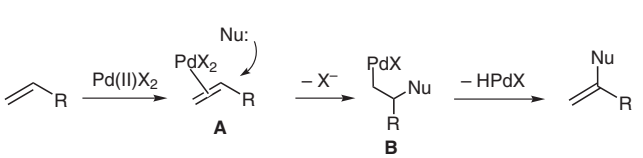
Abstract: The cyclization of *N*-allyl-*N*-carbetoxy-substituted aminothiophenes and furans was performed by intramolecular Pd(II)-catalyzed oxidative coupling. The process involves a nucleophilic attack of a heteroaromatic carbon to the internal carbon of the π-olefin complex through a 5-*exo-trig* ring-formation. Better conditions required $PdCl_2(MeCN)_2$ as catalyst, $CuCl_2$ as co-catalyst and an environmentally friendly reoxidant such as O_2 to promote the catalytic cycle.

Key words: coupling, cyclizations, furans, fused ring systems, palladium

The development of methodologies for the direct functionalization of relatively unreactive C–H bonds has now become a major topic of research.[1] Many of these are promoted by transition metals, among which palladium is the most widely used. In fact, the recent rapid growth of this area is not surprising, since palladium-based methodologies facilitate the direct formation of C–C, C–O, and C–N bonds without utilizing prefunctionalized C–X bonds (X = halogens, OTf). Although the pioneering studies on the activation of inert C–H bonds by stoichiometric amounts of palladium complexes appeared in the early 1960s, it was more than 20 years later that catalytic reactions involving the cleavage of C–H bonds were achieved.[2] From the mechanistic point of view, the crucial step is the attack of the nucleophile to the π-olefin complex **A** giving rise to the σ-alkylpalladium complex **B**, susceptible to β-hydride elimination to furnish a substituted olefin (Scheme 1).

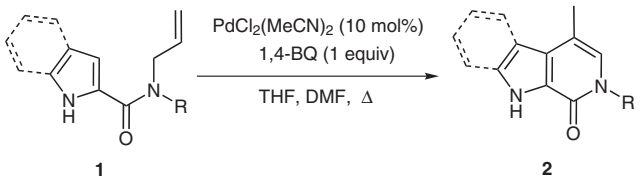
In the field of palladium-catalyzed C–C bond-formation reactions, a relevant role was undertaken by homo- and heterocoupling involving alkenes, arenes, and heteroarenes. In the literature there are some examples of oxidative coupling reactions between alkenes and heteroarenes, involving the most electron-rich carbon atoms of five-membered rings. In particular, indoles and pyrroles have been studied both in intermolecular[3] and intramolecular[4] processes, while the behavior of furan and thiophene has been investigated only in intermolecular reactions.[5]



Scheme 1 General mechanism of Pd(II)-promoted functionalization of unactivated olefins

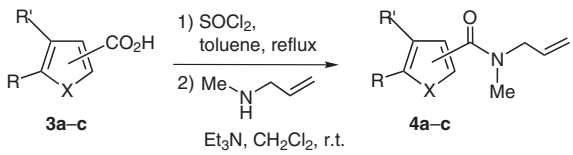
Herein we report the first intramolecular Pd(II)-catalyzed oxidative coupling on variously substituted furan and thiophene rings to access to fused heterocyclic systems.

During our studies on the cyclization of the pyrrole and indole allylamides **1**,[4a,f] we succeeded in the synthesis of pyrido[3,4-*b*]indole and pyrrolo[2,3-*c*]pyridine by the use of $PdCl_2(MeCN)_2$ as catalyst and 1,4-benzoquinone (1,4-BQ) as reoxidant agent (Scheme 2). On the basis of this result, we have undertaken an investigation on the possibility of an analogous intramolecular oxidative coupling on thiophene and furan derivatives having the same functionalization.



Scheme 2 Pd-catalyzed intramolecular cyclization of pyrrole- and indole-allylamides

To this purpose, we prepared the amides **4a–c** from the corresponding carboxylic acids **3a–c** (Scheme 3). The latter were selected in order to test the nucleophilic bent of both α-and β-carbon atoms of the heterocycles.



a: X = S; 2-CO_2H (or 2-allylmethylamide); R = H; R' = Me
b: X = S; 3-CO_2H (or 3-allylmethylamide); R = H; R' = H
c: X = O; 2-CO_2H (or 2-allylmethylamide); R = R' = (CH=CH)$_2$

Scheme 3 Preparation of allylamides **4a–c**

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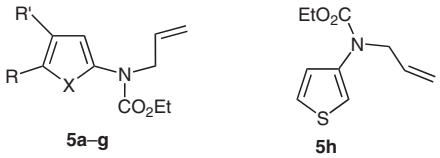
Despite the use of a variety of reaction conditions determined by different combinations of catalyst, oxidant agent, solvent, and temperature, no product of oxidative coupling was observed.

A possible reason of the behavior of the carboxyamides **4a–c** with respect to the pyrrole and indole ones may derive from the less nucleophilic properties of the carbon atoms of the thiophene and furan rings, which are consequently unable to attack the electrophilic π-olefin complex. To support this view, we turned our attention towards thiophene and furan derivatives bearing electron-donor groups, so increasing the electronic density on the ring carbon atoms. We devised as suitable substrates the carbamates **5** (Figure 1), which were synthesized through a four-step sequence from the corresponding carboxylic acids according to the protocol already reported for some of them.[6]

The feasibility of the intramolecular oxidative coupling of these carbamates and the search of better conditions were made on compound **5a**. Actually, we obtained the bicyclic compound **6a** arising from the nucleophilic attack of the heteroaromatic carbon in 3-position to the internal ethylenic carbon, through a 5-*exo-trig* cyclization.[7] Table 1 collects the most representative results of the reaction of **5a** under different conditions.



5a–g **5h**

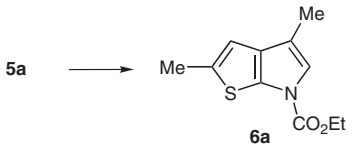
a: X = S, R = Me, R' = H
b: X = S, R = R' = H
c: X = S, R = H, R' = Me
d: X = S, R = R' = (CH=CH)$_2$
e: X = O, R = Ph, R' = H
f: X = O, R = R' = (CH=CH)$_2$
g: X = O, R = R' = H

Figure 1 Thienyl- and furylcarbamate structures

The cyclization process took place only in the presence of $PdCl_2(MeCN)_2$ as catalyst and a Cu(II) salt as oxidant. Better results (entries 6, 8, and 9) were achieved with the combination $PdCl_2(MeCN)_2$ and $CuCl_2$ respectively, as catalyst and oxidant in DMF or MeOH as solvents, even if the former warrants higher yields. $CuCl_2$ acts as reoxidant when used in stoichiometric amount (entry 8) as well as in the role of cocatalyst in the presence of oxygen atmosphere (entries 6 and 9). 1,4-Benzoquinone fails as reoxidant and no improvements were observed by adding organic and inorganic bases or additives such as Bu_4NCl.

Following the protocol of entry 6, i.e. 15 mol% $PdCl_2(MeCN)_2$ and 15 mol% $CuCl_2$ in DMF as solvent in

Table 1 Reaction Conditions for Intramolecular Oxidative Coupling of **5a**

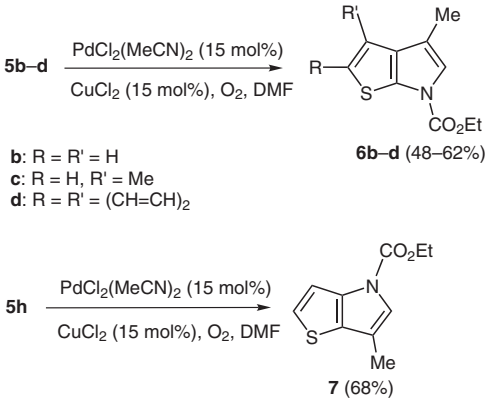


6a

Entry	Catalyst[a]	Oxidant	Solvent	Temp (°C)	Yield (%)
1	$Pd(OAc)_2$	1,4-BQ (2 equiv), O_2	DMSO	100	–
2	$PdCl_2(MeCN)_2$	1,4-BQ (1 equiv)	THF–DMF (2:1)	60	–
3	$Pd(OAc)_2$	MnO_2 (1 equiv), Na_2CO_3 (3 equiv)	DMF	100	–
4	$Pd(OAc)_2$	1,4-BQ (1 equiv), Na_2CO_3 (3 equiv)	DMF	150	–
5	$Pd(OAc)_2$	Na_2CO_3 (3 equiv), $Bu_4N^+Cl^-$ (1 equiv), 1,4-BQ (3 equiv)	DMF	100	–
6	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O_2	DMF	100	70
7	$PdCl_2(MeCN)_2$	$Cu(OAc)_2$, O_2	DMF	100	15
8	$PdCl_2(MeCN)_2$	$CuCl_2$ (3 equiv)	DMF	100	65
9	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O2	MeOH	r.t.	55

[a] $Pd(OAc)_2$ (10 mol%), $PdCl_2(MeCN)_2$ (15 mol%).

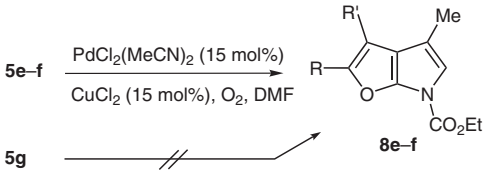
oxygen atmosphere, the carbamates **5b–d** were cyclized to the thieno[2,3-*b*]pyrroles **6b–d**, while carbamate **5h** furnished the thieno[3,2-*b*]pyrrole **7** (Scheme 4). The achievement of derivatives having such skeletons constitutes a valuable target, due to their presence in many patented compounds endowed with anticoagulant,[8] antidiabetic,[9] antihistaminic,[10] anti-inflammatory,[11] and antitumor[12] properties.



Scheme 4 Synthesis of thieno[2,3-*b*]pyrrole and thieno[3,2-*b*]pyrrole derivatives

At this point of our study, having identified the optimal protocol to carry out the intramolecular oxidative coupling on thiophene ring, we extended its use to the cyclization of furan carbamates **5e–g** (Scheme 5). As shown in Table 2, the derivatives **5e**,**f** led to furo[2,3-*b*]pyrroles **8e**,**f**,[13] even if in lower yield than thiophene substrates. However, carbamate **5g** did not give any cyclized product and was recovered unchanged. Attempts to perform the oxidative coupling by changing reaction conditions failed. The behavior of compound **5g** is possibly accounted for by the presence of an unsubstituted α-carbon in the furan ring, resulting in decomposition of starting material.

The plausible mechanism for the intramolecular oxidative coupling just described is exemplified in Scheme 6 for the conversion of carbamate **5a** in the bicyclic product **6a**. In the initial intermediate **C**, the intramolecular nucleophilic attack of the heteroaromatic β-carbon to the π-olefin palladium(II)-complexed portion affords the σ-complex **D**,



Scheme 5 Synthesis of furo[2,3-*b*]pyrrole derivatives

Table 2 Conditions and Cyclization Results of Furylcarbamates **5e–g**

Compd	Catalyst[a]	Oxidant	Solvent[b]	Product (yield)
5e	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O_2	DMF	8e (41%)
5f	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O_2	DMF	8f (23%)
5g	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O_2	DMF	SM[c]
5g	$PdCl_2(MeCN)_2$	$CuCl_2$ (3 equiv)	DMF	SM[c]
5g	$PdCl_2(MeCN)_2$	$CuCl_2$ (15 mol%), O_2	MeOH	tar[d]

[a] 15 mol%.
[b] At 100 °C in DMF, 60 °C in MeOH.
[c] SM: starting material.
[d] Dark tar: unresolved.

which in turn undergoes β-hydride elimination forming the exomethylenic cyclization product **E**. This latter easily isomerizes to the final product **6a** as the consequence of palladium coordination of the exocyclic ethylenic bond followed by β-elimination involving the endocyclic carbon. The catalytic cycle ends on generating Pd(0), which is practically reoxidized to Pd(II) by molecular oxygen via the cocatalytic action of $CuCl_2$.

It remains to be stressed that a pronounced electronic availability of the thiophene or furan ring is essential to the effectiveness of the intramolecular oxidative coupling. In fact, the latter process occurs in the case of substrates **5** bearing an electron-donor substituent on the heterocycle, but is failing in the case of electron-poor systems such as carboxyamides **4**.

In conclusion, we have developed an unprecedented Pd(II)-mediated intramolecular oxidative coupling on thiophene and furan rings to produce thieno- and furopyrrole derivatives of potential interest in pharmacology. In comparison with previously reported methods for the construction of such skeletons, the present protocol is advantageously operative on unfunctionalized ethylenic bonds.[14] Moreover, an environmentally friendly reoxidant such as O_2 is enough to promote the catalytic cycle.

Acknowledgment

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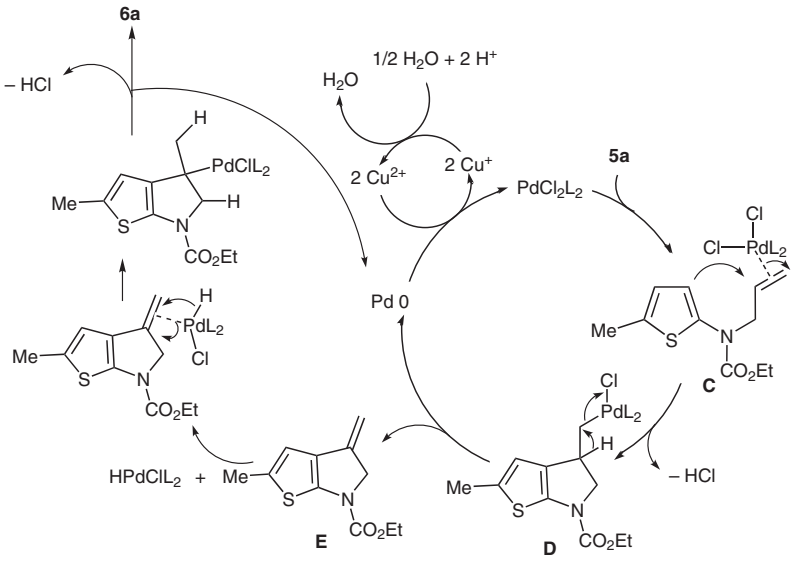

Scheme 6 Catalytic cycle for intramolecular oxidative coupling exemplified on carbamate **5a**

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(7) **Experimental Procedure**
A mixture of $PdCl_2(MeCN)_2$ (39 mg, 0.15 mmol) and $CuCl_2$ (20 mg, 0.15 mmol) in DMF (13 mL) was stirred at r.t. for 30 min under oxygen atmosphere. After addition of a solution of **5a** (225 mg, 1 mmol) in DMF (13 mL), the mixture was heated at 100 °C for 2 h under an O_2 atmosphere. The mixture was washed with brine and extracted with Et_2O (2 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was chromatographed on a silica gel column with light PE–EtOAc (10:1) as eluent to give **6a**.
Data for 6-Carbethoxy-2,4-dimethyl-6*H*-thieno[2,3-*b*]pyrrole (6a)
Oil. IR (nujol): 1635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (3 H, t, *J* = 7.2 Hz), 2.20 (3 H, s), 2.53 (3 H, s), 4.45 (2 H, q, *J* = 7.2 Hz), 6.65 (1 H, s), 7.11 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4 (q), 14.7 (q), 16.3 (q), 63.8 (t), 114.7 (d), 117.7 (s), 120.3 (d), 133 (s), 136.6 (s), 150.1 (s), 162.9 (s). MS: *m/z* 223 [M^+]. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found C, 59.01; H, 6.06; N, 6.41.

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(13) **6-Carbethoxy-4-methyl-2-phenyl-6*H*-furo[2,3-*b*]pyrrole (8e)**
Oil. IR (nujol): 1635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (3 H, t, *J* = 7.1 Hz), 2.19 (3 H, s), 4.50 (2 H, q, *J* = 7.1 Hz), 6.77 (1 H, s), 6.79 (1 H, br s), 7.24–7.26 (1 H, m), 7.40 (2 H, dd, *J* = 7.8, 7.5 Hz), 7.70 (2 H, d, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (q), 14.8 (q), 63.8 (t), 100.2 (d), 115.0 (s), 115.4 (s), 116.0 (d), 123.6 (d), 127.3 (d), 129.1 (d), 131.7 (s), 147.4 (s), 149.4 (s), 154.5 (s). MS: *m/z* = 269 [M^+]. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found C, 71.32; H, 5.80; N, 5.05.

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