Synthesis of 1,2,3,5-Substituted Pyrroles through Palladium-Catalyzed Reaction of Ethyl 2-Acetyl-4-Pentynoate Tosylhydrazone with Aryl Iodides

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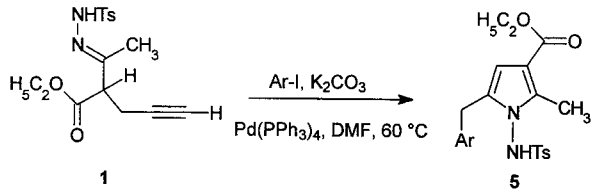
Received 21 July 1997

Abstract. The palladium-catalyzed reaction of the ethyl 2-acetyl-4-pentynoate tosylhydrazone with aryl iodides in the presence of K_2CO_3 and catalytic amounts of a palladium complex affords 1,2,3,5-substituted pyrroles in satisfactory yield.

Pyrrole derivatives represent a class of heterocycles widely spread in nature[1] and substituted pyrroles very frequently display biological activity.[2] Recently 1-aminopyrroles were used as precursors in the synthesis of analgesics[3] and NMDA receptor antagonists.[4] Therefore novel syntheses of functionalized 1-aminopyrroles are of current interest.[5]

In connection with our ongoing activity aimed at developing a general synthetic strategy to reach directly polyfunctionalized pyrrole derivatives,[6] we wish to report that the easily available ethyl 2-acetyl-4-pentynoate tosylhydrazone[7] **1** could be a suitable starting building block of the target polyfunctionalized 1-tosylaminopyrroles **5** (Scheme 1).



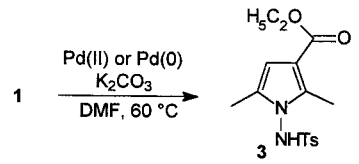
1 **5**

Scheme 1

Indeed we have found that **1** can be treated with aryl iodides **2**, $Pd(PPh_3)_4$ and K_2CO_3 to give **5** in moderate to fair yield (procedure A).[8]

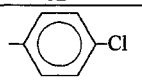
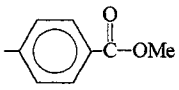
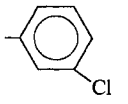
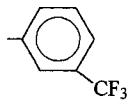
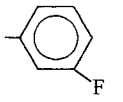
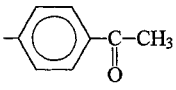
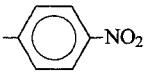
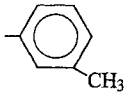
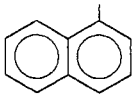
Our results are summarised in Table 1.

The palladium catalyst is essential to make the intramolecular aminopalladation and the cross coupling of the acetylenic hydrazone occur. The implication of a palladium (II) species into the cyclization step is suggested by the observation that the tosylhydrazone **1** can be recovered, under the usual reaction conditions, in the absence of the palladium catalyst and can be converted into the corresponding 1-tosylaminopyrrole **3** on treatment with $K_2CO_3/Pd(OAc)_2$ in DMF (64% yield) or with $Pd(Cl)_2$ in refluxing aqueous acetonitrile according to Utimoto conditions[9] (62% yield) (Scheme 2). Surprisingly, even in the presence of Pd(0) species **1** gave **3** (30% and 36% yield, respectively with $Pd(Ph_3)_4$ and $Pd(dppe)_2$. It can be speculated that this reaction is catalysed by a σ-alkynyl-palladium (II) hydride species generated *in situ* from insertion of the metal into the C_{sp}-H bond of **1**.[10] The insertion of low-valent palladium species into C-H bonds of terminal



Scheme 2

Table 1. Palladium catalyzed-synthesis of 1,2,3,5-substituted pyrroles[a] **5** and **8**

Entry	Procedure	Ar-I Ar- =	Reaction time (h)	% yield of **5**	% yield of **8**
1	A[b]	 **2a**	8	55(10)[c] **5a**	
2	B[d]	"	12		60 **8a**
3	A	 **2b**	2.5	50 **5b**	
4	B	"	12		66(10)[c] **8b**
5	A	 **2c**	6	52(6)[c] **5c**	
6	A	 **2d**	6	48(4)[c] **5d**	
7	A	 **2e**	7	65(5)[c] **5e**	
8	A	 **2f**	4	60 **5f**	
9	A	 **2g**	4	63 **5g**	
10	A	 **2h**	5	70 **5h**	
11	A	 **2i**	5	62 **5i**	
12	A	 2j	5	61 5j	

[a]Yields refer to single runs, are given for isolated products and are calculated on the basis of **1** for the procedure A and on the basis of **2** for the procedure B. All new products had satisfactory elemental analysis and spectral data were consistent with postulated structures; [b]Unless otherwise stated, reactions were carried out at 60 °C in DMF under nitrogen atmosphere using the following molar ratios: **1**:**2**: K_2CO_3:$Pd(PPh_3)_4$=1:2:5:0.02; [c]Yield of **3**; [d]Unless otherwise stated, the reactions were carried out at 60 °C under dry CH_3CN under CO atmosphere using the following molar ratios: **1**:**2**:K_2CO_3: $Pd(OAc)_2$:$P(o\text{-}tol)_3$=1,5:1:5:0.05:0.20

acetylenes leading to the *in situ* generated σ-alkynyl-palladium (II) hydride species has been also invoked in the addition of palladium hydride across the terminal acetylene followed by reductive elimination.[11]

Pyrrole **3** may represent a side product under the usual reaction conditions: the **5** /**3** balance can be primarily affected by the features of the palladium catalyst (Table 2). In essence, by choosing 1-chloro-4-iodobenzene **2a** and **1** as a model system, we found that optimum conditions employed $Pd(PPh_3)_4$ as the palladium source.

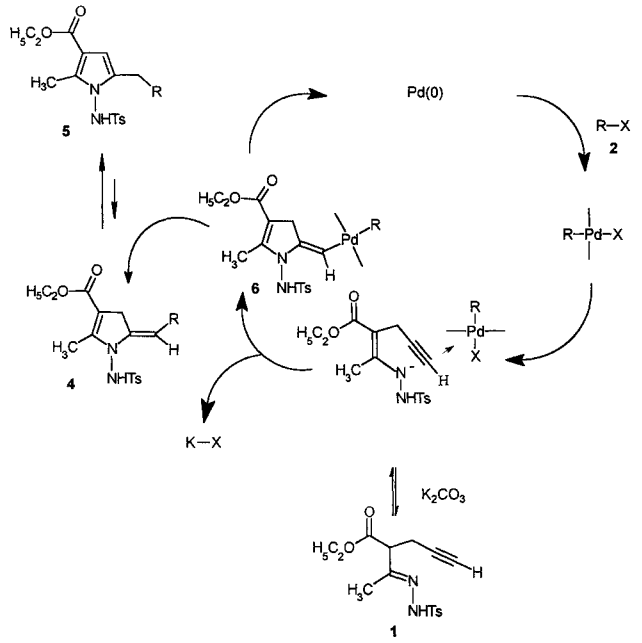
Table 2- Palladium-catalyzed Synthesis of **5a** from **1** and **2a**[a]

entry	catalyst (palladium:ligand ratio)	% yield of **5**[a]	% yield of **3**[a]
a	$Pd(PPh_3)_4$	55	10
b	$Pd(OAc)_2$	-	50
c	$Pd(Cl_2)(PPh_3)_2$	7	30
d	$Pd(OAc)_2$ /P(o-tol)$_3$ (1:4)	20	42
e	$Pd(OAc)_2$ /dppf (1:2)	-	25
f	$Pd(dppe)_2$	15	48

a) Unless otherwise stated, the reactions were carried out at 60 °C in DMF under nitrogen atmosphere using the following molar ratios: **1**:**2**: K_2CO_3: palladium catalyst=1:2:5:0.02; all yields refer to chromatographically purified products and are calculated on the basis of **1**

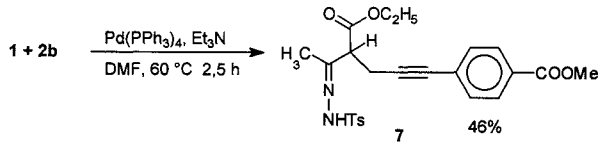
Further work is in progress to shed light on the effects of the ligands on the reaction outcome.

Mechanistically, as suggested for a variety of cyclizations of alkynes containing carbon, oxygen and nitrogen nucleophiles near the carbon-carbon triple bond,[12] the reaction may be supposed to proceed through the following basic steps: a) oxidative addition of Pd(0) to **2** to afford the σ-arylpalladium complex; b) generation of the σ-vinylpalladium complex **6** via regio-chemoselective *trans* addition of the nitrogen and palladium across the carbon-carbon triple bond (*exo-dig* process), c) reductive elimination of Pd(0) to give **4**, and isomerization of **4** to **5** (Scheme 3).



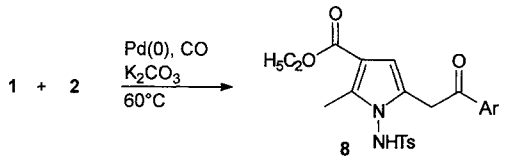
Scheme 3

The synthesis of **7** (Scheme 5) by treatment of **1** with methyl 4-iodobenzoate in the presence of triethylamine instead of potassium carbonate,[13] allows to rule out possible formation of the pyrrole ring of **5** through a mechanism involving cleavage of the C_{sp}-H bond : compound **7** reacted very sluggishly even in the presence of the very reactive catalyst $PdCl_2$ in refluxing aqueous acetonitrile to give the title compound **5b** in 20% yield after 30 hr.



Scheme 4

Moreover the use of $Pd(OAc)_2P(o\text{-}Tol)_3$, as catalytic system, in acetonitrile, under a carbon monoxide atmosphere at 60 °C and a **2**/**1** ratio = 0.66 (procedure B) can make possible the synthesis of **8** (Table 1, entries 2,4) by means of a palladium-catalyzed domino reaction.[14]



Scheme 5

In conclusion, the regioselective heterocyclization described above provides an easy access to functionalized 1-tosylaminopyrroles **5** and **8** and holds promise as a useful and versatile tool for the preparation of this class of compounds. The utility of the present reaction may be apparent from the ready availability of the starting tosylhydrazone **1**.

Acknowledgements. This work was supported by financial assistance from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST-ROMA) and Consiglio Nazionale delle Ricerche (C.N.R.-ROMA). Mr Renato Di Bartolomeo's help and technical assistance is also gratefully acknowledged.

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(7) The preparation of the tosylhydrazone **1** is as follows: to a stirred solution of ethyl 2-acetyl-4-pentynoate (1.19 g, 7.7 mmol) in hot methanol (50 ml) was added *p*-toluenesulfonylhydrazine(1.43 g, 7.7 mmol). The mixture was allowed to cool to room temperature and was magnetically stirred for 24 h. Then the reaction mixture was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel eluting with n-hexane/ EtOAc (70/30 v/v) to give 2.35 g (95 % yield) of **1**: mp 66-69 °C; I.R. (KBr) 3350, 3280, 2120, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.37 (s, 1 H), 7.72 (AA' part of an AA'BB' system, J = 8.9 Hz, 2 H), 7.19 (BB' part of an AA'BB' system, J = 8.9 Hz, 2 H), 3.95 (q, 2H), 3.35 (t, 1 H), 2.49 (m, 2 H), 2.3 (s, 3 H), 1.71 (s, 3 H), 1.69 (t, 1H), 1.06 (t, 3 H) ^{13}C NMR δ 169.9, 152.1, 143.8, 135.1, 128.4, 127.8, 80.3, 70.1, 61.2, 52.7, 21.4, 18.6, 14.8, 13.8; Ms (ESI) M/e/ (relative intensity) 337 $[M+H]^+$ (100).

(8) A typical procedure A is as follows: a solution of **1** (0.23 g, 0.68 mmol) in DMF (3 ml), 1-fluoro-3-iodobenzene **2e** (0.303g,1.37 mmol), K_2CO_3 (0.469 g, 3.4 mmol) and $Pd(PPh_3)_4$ (0.016 g, 0.013mmol) was stirred at 60 °C for 7 h, under nitrogen atmosphere. Then the mixture was cooled, diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with *n*-hexane/ethyl acetate (80/20 v/v) to afford 0.19 g of **5e** (65% yield): mp 49-50 °C; IR (KBr) 3200, 1670, 1580, 1210, 795, 750, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30 (bs, 1H), 7.84 (AA' part of an AA'BB' system, 2 H), 7.27 (BB' part of an AA'BB' system, 2 H), 7.17-6.86 (m, 4 H), 6.12 (s, 1 H), 4.15 (q, 2 H), 3.59 (s, 2 H), 2.44 (s, 3 H), 2.01 (s, 3 H), 1.25 (t, 3 H); ^{13}C NMR δ 165.3, 160.4, 145.7, 145.4, 140.6, 138.3, 137.6, 135.0, 131.8, 130.2, 130.1, 130.0, 128.8, 128.2, 124.3, 115.7, 113.6, 110.4, 107.5, 59.8, 31.5, 21.6, 14.3, 10.78, 10.71,; Ms, m/e (relative intensity) 430 (9), 275(11), 110(100), 91(47).

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