The Palladium-Catalysed Synthesis of 2,3,5-Trisubstituted Furans from 2-Propargyl-1,3-dicarbonyl compounds and Vinylic or Aryl Triflates or Halides.

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Abstract: The palladium-catalysed cyclization of 2-propargyl-1,3-dicarbonyl compounds with vinylic or aryl triflates or halides in the presence of potassium carbonate produces 2,3,5-trisubstituted furans in good yield.

Furans represent one of the most common of the five-membered oxygen-containing heterocyclic ring systems and can be found in a large number of natural substances[1] and in important pharmaceuticals.[2] Furthermore, polysubstituted furans are useful building blocks in organic synthesis.[3] Our interest in developing new general procedures for the synthesis of five-membered oxygen heterocycles[4] and the successful preparation of (E)-δ-substituted-γ-methylene-γ-butyrolactones[4b] and 2,3-disubstituted indoles[5] from functionalized alkynes and vinyl triflates or aryl halides prompted us to investigate the possible extension of this methodology to the preparation of 2,3,5-trisubstituted furans. 2,3,5-Trisubstituted furans may be in fact valuable intermediates for the preparation of complex molecules. For example, strategies for the total synthesis of pseudopterolide and allied pseudopterans[3c] and furanocembranolides[3d] based on the elaboration of suitable 2,5-disubstituted-3-carbomethoxy-furans have been recently presented.
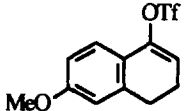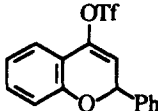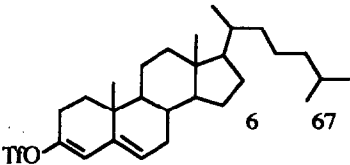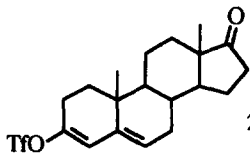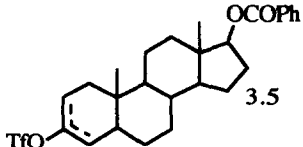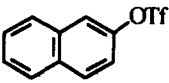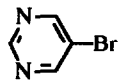
Easily available[6] 3-acetyl-5-hexyn-2-one **1a** and ethyl 2-acetyl-4-pentynoate **1b** have been selected as the functionalized alkynes. Herein we report that the reaction of **1** with vinylic or aryl triflates or halides in the presence of tetrakis(triphenylphosphine)palladium(0) and K_2CO_3 provides a general route to the synthesis of 2,3,5-trisubstituted furans **3**. Our results are summarized in the Table.
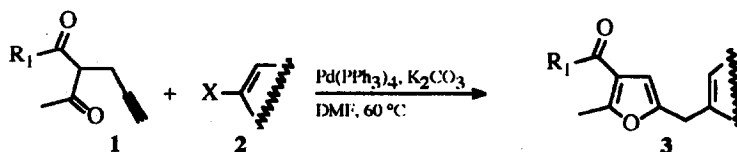
1a: R_1 = Me
1b: R_1 = EtO
X = I, Br, OTf

Scheme 1

Table. Palladium-Catalysed Synthesis of 2,3,5-Trisubstituted Furans **3** from 2-Propargyl-1,3-dicarbonyl compounds **1**.[a,b]

| entry	starting alkyne 1	organic triflate or halide 2	reaction time (h)	yield % 3	entry	starting alkyne 1	organic triflate or halide 2	reaction time (h)	yield % 3
a	1a	(MeO-substituted dihydronaphthalenyl OTf)	1.5	66	h	1a	(chromene OTf, Ph)	2.5	67
b	1a	(cholesteryl TfO)	6	67	i	1a	(steroidal ketone TfO)	2.5	56
c	1a	PhCH=CHBr[c]	7	51					
d	1a	4-MeOOC-C₆H₄-I	1.5	56					
e	1a	4-Cl-C₆H₄-I	1.5	52					
f	1a	PhI	6	57 (25)[d]	j	1b	(steroidal OCOPh TfO)	3.5	75
g	1a	(pyrimidinyl-Br)	3	62[e]	k	1a	(naphthalenyl OTf)	2.5	71
					l	1b	"	7	55

[a] Unless otherwise stated, reactions were carried out at 60 °C in DMF in the presence of an excess of K_2CO_3 under a nitrogen atmosphere using the following molar ratios: 1: vinylic or aryl halide: $Pd(PPh_3)_4:K_2CO_3$ = 1: 2: 0.02: 5 or 1: vinylic or aryl triflate: $Pd(PPh_3)_4: K_2CO_3$ = 1.3: 1: 0.02: 5. [b] Yields refer to single runs, are given for pure isolated products, and are based on either 1 (in the reactions of vinylic or aryl halides) or on the vinylic or aryl triflate. [c] A commercially available E/Z mixture of β-bromostyrene was used. Only the product containing the E-styryl moiety was isolated. [d] In the presence of $Pd(OAc)_2(PPh_3)_2$. [e] 90 °C.

A typical procedure is as follows: to a solution of **1a** (0.261 g, 1.89 mmol) in DMF (4 ml), methyl 4-iodobenzoate **2d** (0.991 g, 3.78 mmol), potassium carbonate (1.3 g, 9.45 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.042 g, 0.038 mmol) were added. The reaction mixture was gently purged with nitrogen and stirred at 60 °C for 3.5 h under a nitrogen atmosphere. Then, diethyl ether and 0.1 N HCl were added; the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 95/5 n-hexane/EtOAc mixture to give **3d** (0.290 g, 56% yield); mp = 69-70 °C (CH_2Cl_2/petroleum ether); IR (KBr) 1710, 1650, 1265, 845, 735, 695 cm⁻¹; ¹H NMR ($CDCl_3$) δ 8.00-7.96 (m, 2 H), 7.31-7.27 (m, 2 H), 6.24 (s, 1 H), 3.94 (s, 2 H), 3.88 (s, 3 H), 2.51 (s, 3 H), 2.33 (s, 3 H); ¹³C NMR ($CDCl_3$) δ 193.9, 166.7, 157.6, 151.4, 142.7, 128.9, 128.8, 107.3, 52.0, 34.1, 29.0, 14.3; MS m/e : 272 (M⁺), 241.

Mechanistically, as suggested for a variety of cyclizations of alkynes containing carbon,[7] oxygen,[4b,8] and nitrogen[5,9] nucleophiles near the carbon-carbon triple bond, the present reaction may proceed through (1) formation of the π-palladium complex **4**, (2) generation of the σ-vinylpalladium complex **5** via regioselective trans addition of the oxygen and palladium across the carbon-carbon triple bond (exo-dig process), (3) reductive elimination of Pd(0) to give **6**, and (4) isomerization of **6** to **3** (Scheme 2).
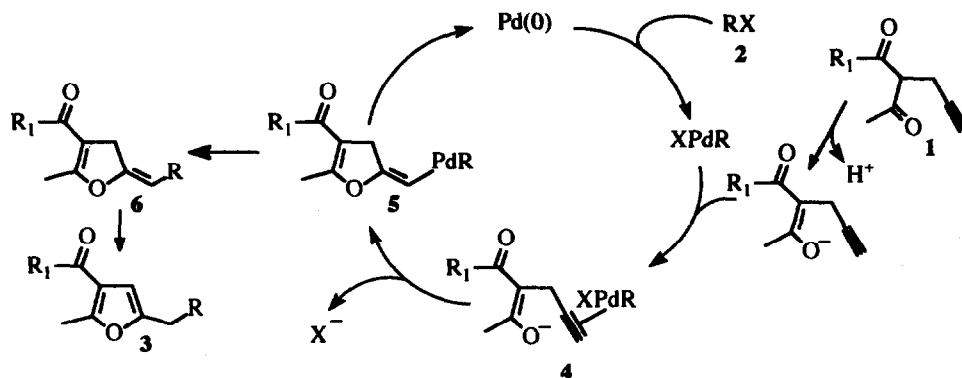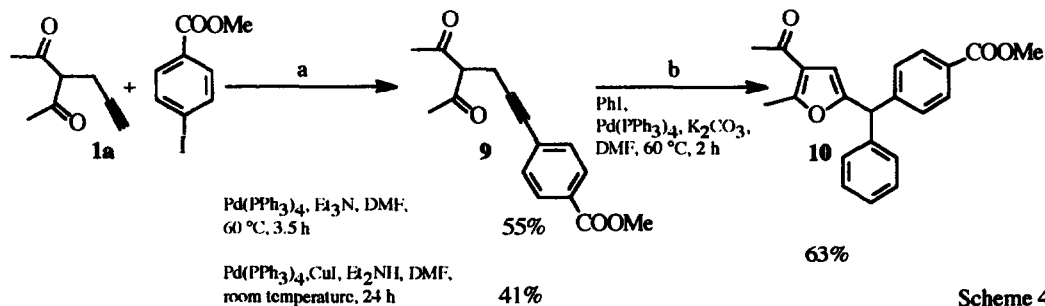
Scheme 2

Isolation of the deuterio derivative **8** (47% yield) from the reaction of 6-deuterio-3-acetyl-5-hexyn-2-one **7**[10] with methyl 4-iodobenzoate rules out possible formation of the furan ring through a mechanism involving cleavage of the C_{sp}-H bond.
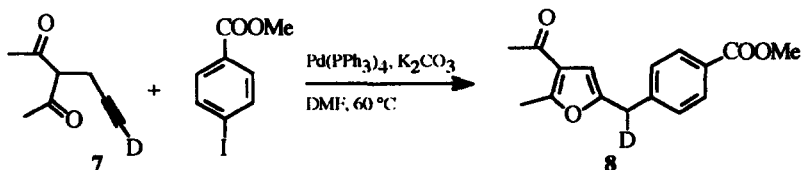
Scheme 3

However, available data do not allow us to exclude the generation of **3** through (1) syn addition of the σ-vinylic- or σ-arylpalladium complex to the carbon-carbon triple bond, (2) nucleophilic attack of the oxygen on the palladium atom to give a six-membered ring, oxygen-containing palladacycle, (3) Pd(0) reductive elimination, and (4) isomerization.[11]

The nature of the base strongly affects the reaction course. When **1a** was reacted with methyl 4-iodobenzoate as usual, in the presence of triethylamine instead of potassium carbonate, the coupling product **9** was isolated in 55% yield, while the furan derivative was formed in only trace amounts.

Scheme 4

Assuming that the π-complex **4** represents an intermediate common both to the pathway producing furan derivatives and to the one producing coupling products[12] and that changing from potassium carbonate to

triethylamine does not significantly change the nature of this complex (in the region covering the carbon-carbon triple bond, the palladium atom, the counterion, and the ligands), the coupling/cyclization balance should be primarily affected by the strength of the nucleophile near the multiple bond. In practice, in the presence of a strong nucleophile, the π-complex 4 tends to undergo preferentially an intramolecular cyclization reaction whereas in the presence of a weak nucleophile the carbon-carbon triple bond in the π-complex is activated towards basic attack on the terminal hydrogen. In this last case, the formation of coupling products is favoured. If this reasoning is correct, it can be inferred that with potassium carbonate, a stronger nucleophile, quite probably an enolate anion generated before coordination, is responsible for the cyclization reaction, while with triethylamine, most of the nucleophile is in the unionized form and the formation of the coupling derivative prevails.

Compound 9 has been successfully employed in the cyclization to the furan derivative 10 (Scheme 4). It is worth noting that the reaction of 1a with methyl 4-iodobenzoate in the presence of Pd(PPh$_3$)$_4$ (0.02 equiv), CuI (0.01 equiv), and Et$_2$NH produced 9 in only 41% yield, together with 2,5-dimethyl-3-acetyl-furan (30% yield), most likely derived from the copper catalysed cyclization[13] of 1a (methyl 4-iodobenzoate was recovered in 36% yield).[14]

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13. For copper catalysed cyclization of alkynes containing carbon nucleophiles near the carbon-carbon triple bond, see: Monteiro, N.; Balme, G.; Gore, G. *Synlett* **1992**, 227-228.

14. When the same reaction was carried out omitting the palladium catalyst and methyl 4-iodobenzoate (24 h), 2,5-dimethyl-3-acetyl-furan was isolated in 50% yield.