Pergamon

Tetrahedron Letters 39 (1998) 5101–5104

TETRAHEDRON LETTERS

2-Substituted-3-allenyl-benzo[*b*]furans through the Palladium-Catalysed Cyclization of Propargylic *o*-(Alkynyl)phenyl Ethers.

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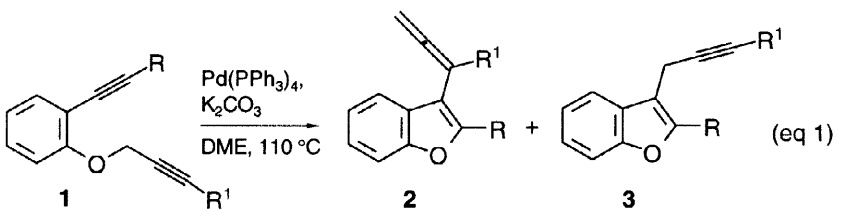
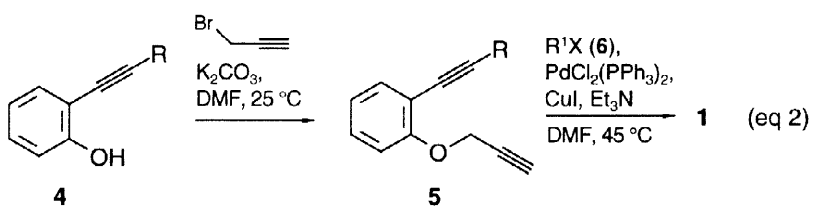
Received 31 March 1998; accepted 5 May 1998

Abstract. The reaction of propargylic *o*-(alkynyl)phenyl ethers in the presence of $Pd(PPh_3)_4$ and K_2CO_3 affords 2-substituted-3-allenylbenzo[*b*]furans in good yields. Depending on the nature of the starting alkyne, variable amounts of isomeric 2-substituted-3-propargylbenzo[*b*]furans have been isolated.

The cyclization of alkynes containing nucleophiles close to the carbon-carbon triple bond promoted by organopalladium complexes has proved to be a powerful tool for the preparation of cyclic derivatives.[1] Our continuing interest in this field and our successful utilization of readily available *o*-alkynyl-N-allyltrifluoroacetanilides and allylic *o*-(alkynyl)phenyl ethers as convenient precursors for the regioselective synthesis of 3-allylindoles[2] and 3-allylbenzo[*b*]furans[3] encouraged us to explore the extension of this methodology to the propargylic *o*-(alkynyl)phenyl ethers **1**. We now report our preliminary results on the conversion of **1** into the 3-allenylbenzo[*b*]furans **2** (eq 1).

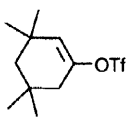
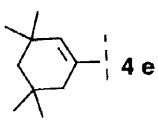


The starting propargylic *o*-(alkynyl)phenyl ethers **1** have been prepared from *o*-alkynylphenols **4** according to the sequence outlined in eq 2, through a one-pot protocol (Table 1)[4] which usually gives better results than the stepwise procedure. For example, **1a** was isolated in 76% yield when it was prepared omitting the isolation of **5a** and in an overall 60% yield (propargylation: 83% yield; palladium-catalysed coupling: 73% yield) following the stepwise protocol.



0040-4039/98/$19.00
PII: S0040-4039(98)00936-8

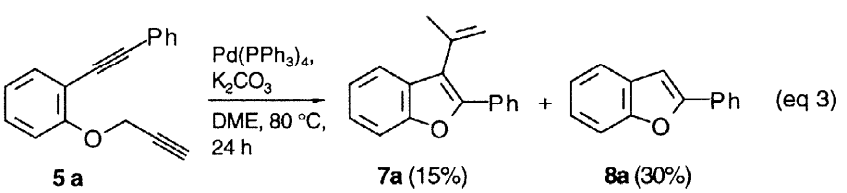
Table 1. Preparation of the Propargylic *o*-(Alkynyl)phenyl Ethers **1**.

entry	*o*-alkynylphenol **4** R	R^1X **6**	propargylic *o*-(alkynyl)phenyl ether **1**	yield % (time)[a]
1	Ph **4a**	*p*-Me-C_6H_4-I	**1a**	76 (1.0 h)
2	**4a**	*p*-MeO-C_6H_4-I	**1b**	80 (2.5 h)
3	**4a**	*p*-MeCO-C_6H_4-I	**1c**	78 (2.5 h)
4	**4a**		**1d**	69 (4.0 h)
5	n-C_5H_{11} **4b**	PhI	**1e**	75 (2.0 h)
6	*p*-MeO-C_6H_5 **4c**	*p*-Me-C_6H_4-I	**1f**	63 (3.0 h)
7	*p*-MeCO-C_6H_4 **4d**	*p*-Me-C_6H_4-I	**1g**	64 (4.0 h)
8	 **4e**	PhI	**1h**	62 (3.0 h)

[a] Yields refer to single runs and are given for pure, isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures.

For the cyclization step we employed the reaction conditions that gave good results in the cyclization of allylic *o*-(alkynyl)phenyl ethers [$Pd(PPh_3)_4$ and K_2CO_3 in DME],[3] at higher temperature. Generally, a temperature of 110 °C has been used. Under these conditions, **1a**, our model system, gave the cyclization derivatives in 90% yield (36 h) as an approximately 73:27 **2a**:**3a** isomeric mixture. At 80 °C **1a** was recovered essentially unchanged after 12 h. Increasing the reaction temperature to 130 °C (diethoxyethane, 2 h) led to the isolation of cyclization products in lower yield (61%; **2a**:**3a** = 72:28). The employment of the $Pd_2(dba)_3$/ttmpp [tris(2,4,6-trimethoxy phenyl)phosphine] combination, which afforded the best results in term of yield and regioselectivity in the cyclization of allylic *o*-(alkynyl)phenyl ethers resulted in the recovery of the starting alkyne in 97% yield (DME, 110 °C, 24 h).[5]

The presence of a substituent on the terminal acetylenic carbon of the propargylic fragment of **5** was found to be crucial for the success of the reaction. Subjection of **5a** to cyclization conditions resulted in the formation of **7a** and **8a**; none of the allenyl and/or propargylic product was observed (eq 3).



5a **7a** (15%) **8a** (30%) (eq 3)

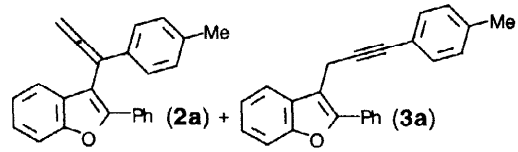
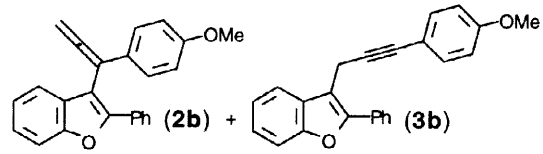
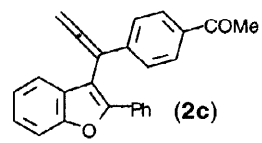
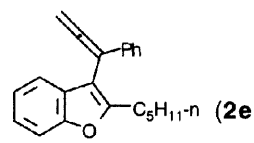
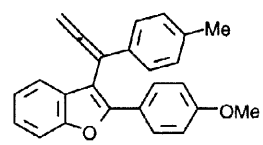
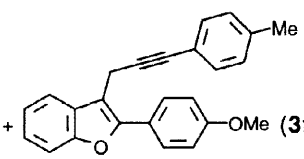
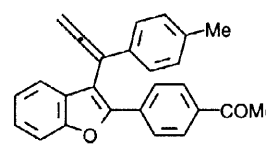
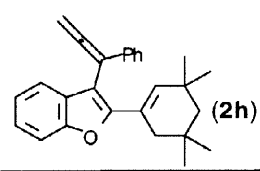
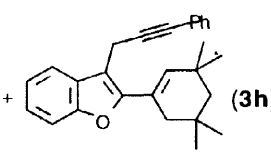
The results obtained in the cyclization of some propargylic *o*-(alkynyl)phenyl ethers **1** are reported in Table 2.

A mechanistic proposal for the present cyclization is outlined in eq 4. The initial cleavage of the O-$C_{propargylic}$ bond through a S_N2' reaction of the Pd(0) complex generates the σ-allenylpalladium phenoxide **9** which can undergo the displacement of one ligand to the palladium by the acetylenic moiety to give **11** or/and isomerise to the propargylic complex **10**, from which **12** is formed. The intermediates **11** and **12** (possibly in equilibrium) next undergo the nucleophilic attack of the oxygen across the activated carbon-carbon triple bond[6]

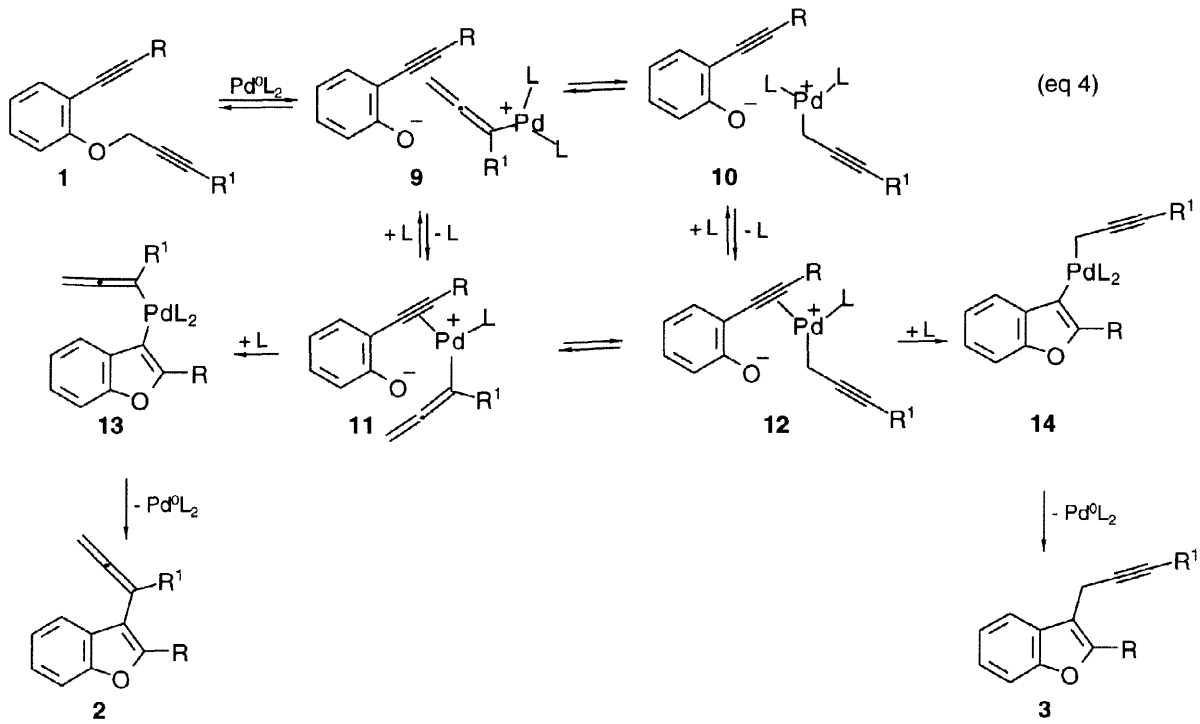
to afford **13** and **14** that subsequently produce the benzo[*b*]furan derivatives **2** and **3**, respectively, through the reductive excision of Pd(0).

In conclusion, we have developed an efficient approach to the synthesis of the unusual class of 3-allenyl-2-substituted-benzo[*b*]furans that stresses further the potential of the cyclization of alkynes containing proximate nucleophiles promoted by organopalladium complexes and can provide a strong stimulus for further functionalization of the benzo[*b*]furan skeleton.

Table 2. Cyclization of Propargylic *o*-(Alkynyl)phenyl Ethers **1**.

entry	**1**	reaction time	cyclization products	% yield[a] (ratio)[b]
1	**1a**	36 h	 **(2a)** + **(3a)**	90 (73:27)[c]
2	**1b**	48 h	 **(2b)** + **(3b)**	61 (75:25)
3	**1c**	36 h	 **(2c)**	53
4	**1d**	12 h		-[d]
5	**1e**	18 h	 **(2e)**	52
6	**1f**	24 h	 **(2f)** +  **(3f)**	86 (85:15)
7	**1g**	48 h	 **(2g)**	57
8	**1h**	48 h	 **(2h)** +  **(3h)**	52 (35:65)

[a] Yields refer to single runs and are given for isolated products. All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and MS analysis. [b] Isomeric ratios were calculated by NMR analysis. [c] The same isomeric ratio was observed after isolation of pure **2a** and **3a** and by NMR analysis of the reaction mixture after workup. [d] **1d** was recovered in 56% yield.



References and Notes

1. For a recent leading reference, see: (a) Cacchi, S.; Fabrizi, G.; Marinelli, F, Moro, L.; Pace, P. *Synlett* **1997**, 1363. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (c) Bouyssi, D.; Cavicchioli, M.; Balme, G. *Synlett* **1997**, 944. (d) Arcadi, A. *Synlett* **1997**, 941. (e) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315. (f) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (g) Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463. (h) Arcadi, A.; Rossi, E. *Tetrahedron Lett.* **1996**, *37* , 6811. (i) Saulnier, M.G.; Frennesson, D.B.; Deshpande, M.S.; Vyas, D.M. *Tetrahedron Lett.* **1995**, *36*, 7841. (j) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (k) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403. (l) Arcadi, A.; Cacchi, S.; Larock, R.C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813. (m) Bouyssi, D.; Gore, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129.
2. Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *62*, 1001.
3. Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* submitted.
4. One-pot reactions have been carried out as follows: *propargylation* [anhydrous DMF (10 mL), room temperature, 1 h]: **1**:propargyl bromide:K_2CO_3 = 5.15 mmol:7.73 mmol:15.46 mmol; *coupling*: after workup, the residue derived from the propargylation step was dissolved in Et_3N (5 mL) and DMF (1 mL), then ArI (6.70 mmol), CuI (0.21 mmol) and $PdCl_2(PPh_3)_2$ (0.11 mmol) were added under argon. The reaction mixture was stirred at 45 °C for 1-4 h and worked-up.
   Attempts to prepare 2-substituted-3-allenylbenzo[*b*]furans through the palladium-catalysed reaction of *o*-alkynylphenols with propargyl carbonates met with failure. For example, subjection of **4a** to 3-(*p*-methylphenyl)-propargyl ethyl carbonate in the presence of $Pd_2(dba)_3$ and ttmpp in DME at 60 °C for 6 h produced **2a** and **3a** in 6 and 2% yield, respectively, along with other unidentified products.
5. Typical procedure for the cyclization of propargylic *o*-(alkynyl)phenyl ethers **1**. A mixture of **1a** (0.100 g, 0.31 mmol), K_2CO_3 (0.210 g, 1.55 mmol) and $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol) in anhydrous DME (3 mL) was stirred at 110 °C for 36 h. Then, diethyl ether and water were added, the organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel) eluting with a *n*-hexane/EtOAc (99/1 v/v) mixture to give 0.066 g (66% yield) of **2a** and 0.024 g (24% yield) of **3a**. **2a**: oil; IR (liquid film) 1935, 1453, 878, 744 cm^{-1}; ^1H NMR δ 7.92 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.39-7.01 (m, 10 H), 5.12 (s, 2 H), 2.31 (s, 3 H); ^{13}C NMR δ 209.4, 154.1, 151.8, 137.2, 131.6, 130.6, 130.2, 129.4, 128.9, 128.6, 128.4, 126.7, 126.6, 124.7, 122.9, 120.6, 111.0, 99.4, 78.0, 21.2; MS *m/e* (relative intensity) 322 (M^+, 68), 307 (100); Anal. Calcd for $C_{24}H_{18}O$: C, 89.40; H, 5.36. Found: C, 89.45; H, 5.41; **3a**: oil; IR (liquid film) 1456, 789 cm^{-1}; ^1H NMR δ 7.92-7.81 (m, 3 H), 7.81-7.27 (m, 9 H), 7.09 (d, J = 8.0 Hz, 1 H), 4.04 (s, 2 H), 2.34 (s, 3 H); ^{13}C NMR δ 154.0, 137.9, 131.5, 130.6, 129.7, 129.0, 128.8, 128.6, 127.4, 124.6, 122.7, 120.3, 119.9, 111.2, 85.7, 81.3, 21.4, 15.4; MS *m/e* (relative intensity) 322 (M^+, 100), 231 (51); Anal. Calcd for $C_{24}H_{18}O$: C, 89.40; H, 5.36. Found: C, 89.43; H, 5.39.
6. For other cyclizations promoted by σ-allenylpalladium complexes, see: Bouyssi, D.; Gore, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129.