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Palladium(II) chloride catalyzes the cross-coupling reaction of 2,5-bis-(butyltelluro)-furan and 1-alkynes

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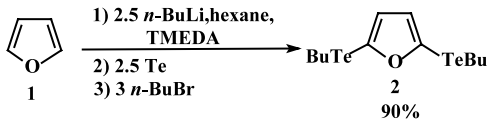
Abstract—Palladium(II) chloride catalyzed the cross-coupling reaction of 2,5-bis-(butyltelluro) furan and terminal alkynes yielding both symmetrically and unsymmetrically substituted 2,5-bis-acetylenic furan derivatives. The methodology represents a general and efficient protocol for carrying out the synthesis of furan derivatives with potential biological activities. © 2003 Elsevier Science Ltd. All rights reserved.

Aromatic heterocyclic compounds such as thiophene, furan, and pyrrole are important structural fragments present in many pharmaceutical and chemical compounds.[1] Furans and their derivatives are also very useful starting materials in the industrial production of important compounds.[2] Further, they play an important role as intermediates in many synthetic pathways, primarily because they react as a special class of vinyl ethers[3] or as dienophiles in the Diels–Alder reaction.[4] The benzofuran ring system is a commonly encountered heterocycle that is found in many natural products and synthetic drug molecules.[5] The biological profile of these agents is broad and depends on the nature and position of the substituents. For example, 5-methoxybenzofuran is a benzofuran with significant antibacterial properties, while 5-tetradecyloxy-2-acetylfuran is reported to be a potent inhibitor of rhinovirus.[5b–d] A plethora of other biological activities has been attributed to benzofurans, the best documented being their antioxidant[6] and anti-inflammatory effects.[7]

The synthesis of polysubstituted furans continues to attract the interest of many synthetic chemists.[8] More recently, we have demonstrated that Pd(II)-catalyzed cross-coupling reaction of 2-(butyltelluro)furan and 1-alkynes produces the corresponding monosubstituted acetylenic furans in high yields.[9] We now wish to report an additional use of this methodology in the cross-coupling reaction of 2,5-bis-(butyltelluro) furan and 1-alkynes.

The starting material required for the coupling, 2,5-bis-(butyltelluro) furan **2**, was synthesized by metalation of furan **1** with *n*-butyllithium.[10] Treatment of 2,5-dilithio-derivative with elemental tellurium and subsequent addition of *n*-butyl bromide gave **2** in good yield[11] (Scheme 1). This compound is stable and can be chromatographed and stored in the freezer for several days.

Since our initial studies have focused on the development of an optimum set of reaction conditions, the coupling reaction of **2** with terminal acetylenes was examined in order to optimize the reaction conditions. In this way, **2** (1 equiv.) and an excess of 2-propyn-1-ol (4 equiv.) in methanol were treated at room temperature with different palladium catalysts. We found that the use of $Pd(PPh_3)_4$, $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$ afforded a little if any of the desired coupling product (Table 1). The reaction was greatly enhanced by using $PdCl_2$ from 3 to 20% (entries 7–10), this fact is in agreement with our previous work, where we found that the $PdCl_2$ is more efficient to



Scheme 1.

Keywords: tellurium; cross-coupling; palladium; furan.
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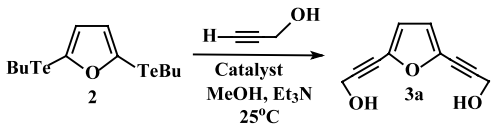
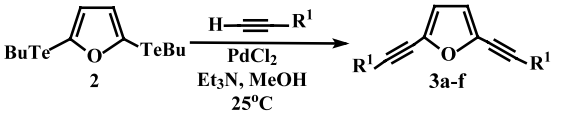
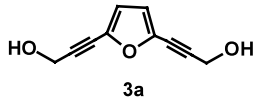
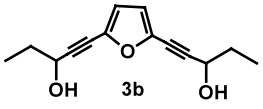
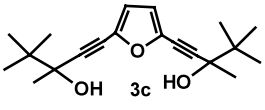
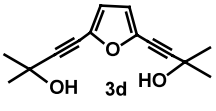
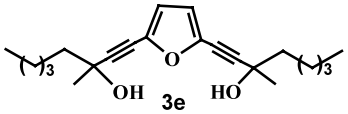
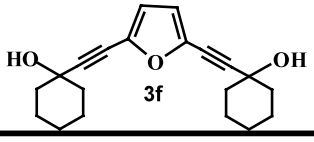
Table 1. Cross-coupling reaction of **2** with propyn-1-ol: influence of palladium catalyst



Entry	Catalyst (mol%)	Time (h)	Yield, **3a** (%)
1	$Pd(PPh_3)_4$ (20)	48	0
2	$Pd(PPh_3)_4$/CuI (20)	48	0
3	$Pd(OAc)_2$ (20)	20	10
4	$PdCl_2(PPh_3)_2$ (20)	20	13
5	$PdCl_2(PhCN)_2$ (20)	24	5
6	$PdCl_2/PPh_3$ (20)	20	15
7	$PdCl_2$ (3)	24	30
8	$PdCl_2$ (5)	24	47
9	$PdCl_2$ (10)	6	72
10	$PdCl_2$ (20)	6	87
11	$PdCl_2$ (20)/CuI (20)	6	85

Table 2. $PdCl_2$ catalyzed cross-coupling of **2** and acetylenes



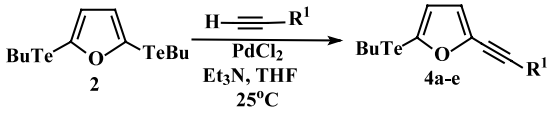
Entry	2,5-bis-acetylenic furan **3**	Time (h)	Yield (%)
1	 **3a**	5	87
2	 **3b**	4	80
3	 **3c**	4	77
4	 **3d**	5	82
5	 **3e**	6	85
6	 **3f**	3	70

perform the coupling reaction.[9] Furthermore, we observed that the addition of copper(I) iodide, promoted a conversion of 85% (Table 1, entry 11) instead 87% (Table 1, entry 10) without any acceleration of the reaction.

The influence of the nature of the amine is noteworthy. When the reaction was performed using pyrrolidine, piperidine or morpholine (1 equiv.) no reaction was observed. The use of Et_2NH, *n*-$PrNH_2$ or *n*-$BuNH_2$ gave the desired product in low yield (20–35%). However, by using Et_3N, **3a** was obtained in good yield. We also found that the yields of product were markedly decreased using DMF, CH_3CN, THF or CH_2Cl_2, instead of MeOH as the solvent. In our experiments the optimum condition for the coupling was $PdCl_2$ (20 mol%), MeOH (5 mL), 2,5-bis-(butyltelluro) furan **2** (1 mmol), the appropriate 1-alkyne (4 mmol) and Et_3N (0.8 mL) at 25°C. By extending the coupling reaction to other alkynes, various 2,5-bis-acetylenic furans **3** were obtained in good yields[12] (Table 2). The formation of the products was confirmed by the analysis of the ^1H NMR and ^{13}C NMR spectra.

In the same way, when the cross-coupling reaction of **2** (1 equiv.) was realized using one equivalent of 1-alkynes instead four equivalents and using THF instead methanol, as described above, the 2-(butyltelluro)-5-(acetylenic) furans **4a–e** were obtained in good yield after purification[13] (Table 3). Analysis of the ^1H NMR and ^{13}C NMR spectra showed that all the 2-(butyltelluro)-5-(acetylenic) furans presented analytical and spectroscopic data in full agreement with their assigned structures.

Table 3. $PdCl_2$ catalyzed the formation of 2-(butyltelluro)-5-(acetylenic) furans **4**



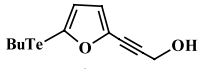
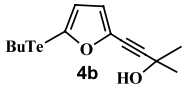
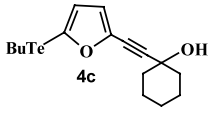
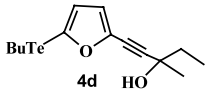
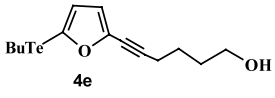
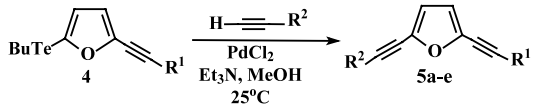
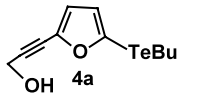
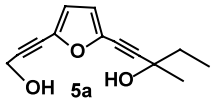
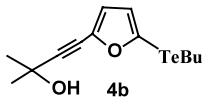
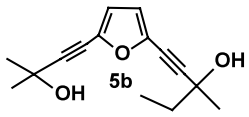
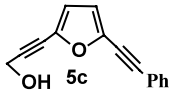
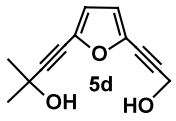
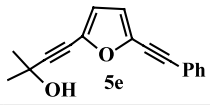
Entry	2-(butyltelluro)-5-(acetylenic) furan **4**	Time (h)	Yield (%)
1	 **4a**	6	82
2	 **4b**	5	83
3	 **4c**	3	78
4	 **4d**	4	77
5	 **4e**	5	87

Table 4. $PdCl_2$ catalyzed the formation of unsymmetrically 2,5-bis-(acetylenic) furans **5**



#	2-(butyltelluro)-5-(acetylenic) furan **4**	2,5-bis-(acetylenic) furan **5**	Time (h)	Yield (%)
1			8	62
2			7	68
3	**4a**		5	65
4	**4b**		7	71
5	**4b**		6	73

Further, we observed that the treatment of 2-(butyltelluro)-5-(acetylenic) furan **4** with terminal alkynes, using the same catalytic system for the cross-coupling reaction described in Table 2, led to the unsymmetrically substituted acetylenic furan derivatives, **5** in excellent yields[14] (Table 4). These compounds can be chromatographed and their structures were confirmed by the analysis of the ^1H NMR and ^{13}C NMR spectra

Acknowledgements

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10. Chadwick, D. J.; Will be, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887–893.
11. **Typical procedure for the preparation of 2,5-bis-(butyltelluro) furan 2:** To a two-necked round-bottomed flask under argon atmosphere containing a solution of furan (20 mmol, 1.36 g) in freshly distilled dry THF (100 mL) and TMEDA (50 mmol, 5.8 g) at room temperature, was added *n*-butyllithium (50 mmol, 1.5 M in hexane, 33.3 mL). The mixture was refluxed for 30 minutes and cooling down to 25°C. Elemental tellurium (50 mmol, 6.35 g) was added in one portion and the mixture was stirred until all the Te has disappeared. The reaction was cooled to 0°C and then *n*-butyl bromide (25 mmol, 6.86 g) was added and the mixture was stirred for 6 h at room temperature. After this period, the reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane, yielding **2** (0.39g, 90%). ^1H NMR (200 MHz, $CDCl_3$) δ 6.30 (s, 2H), 2.49 (t, 7.2 Hz, 4H), 1.45 (m, 4H), 1.11 (m, 4H), 0.52 (t, 7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 126.98, 124.12, 33.66, 24.55, 13.21, 10.22. MS *m*/*z* (%) 433 (50), 377 (15), 250 (100), 193 (47), 66 (32), 57 (84).

12. **Typical procedure for 2,5-bis-(alkynyl) furans 3:** To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension of $PdCl_2$ (0.035 g, 20 mol%) in dry methanol (5 mL) was added **2** (0.434 g, 1 mmol). After stirring for 15 minutes at room temperature, the appropriate alkyne (4 mmol) and Et_3N (0.8 mL) were successively added. The reaction was stirred at room temperature for the time indicated in Table 2. After this period the mixture was filtered under vacuum and the filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (20:80). **3a:** Yield: 0.153 g (87%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.53 (s, 2H); 4.42 (s, 4H); 2.05 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 136.96; 116.49; 92.30; 75.54; 51.38. MS m/z (%) 176 (34), 159 (12), 141 (70), 121 (100), 66 (76). IR (KBr, film) ν 3500–3100 (O–H), 3097, 1921, 2859, 2213, 1506, 1429, 1206, 864.
13. **General procedure for 2-(telluro)-5-(alkynyl) furans 4:** To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension $PdCl_2$ (0.035 g, 20 mol%) in dry THF (5 mL) was added **2** (0.434 g, 1 mmol). After stirring for 15 minutes at room temperature, the appropriate acetylene (1 mmol) and Et_3N (0.8 mL) were successively added. The reaction was stirred at room temperature for the time indicated in Table 3, and then filtered under vacuum. The filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (80:20). **4a**: Yield: 0.250 g (82%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.63 (d, 3.2 Hz, 1H), 6.45 (d, 3.2 Hz, 1H), 4.44 (s, 2H), 2.77 (t, 7.4 Hz, 2H), 1.73 (qui, 7.4 Hz, 2H), 1.30 (sex, 7.4 Hz, 2H), 1.26 (s, 1H), 0.87 (t, 7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.88, 126.14, 120.45, 117.38, 93.19, 75.52, 52.31, 33.83, 24.72, 14.08, 10.18. MS m/z (%) 305 (12), 252 (30), 121 (42), 105 (100), 66 (98), 57 (60). IR (KBr, film) ν 3500–3100 (O–H), 3043, 2960, 2835, 1237, 1542, 1437, 1248, 861.
14. **General procedure for 2,5-bis-(alkynyl) furans 5:** To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension $PdCl_2$ (0.035 g, 20 mol%) and dry methanol (5 mL) was added **4** (1 mmol). After stirring for 15 minutes at room temperature, the appropriate acetylene (2 mmol) and Et_3N (0.8 mL) were successively added. The reaction was stirred at room temperature for the time indicated in Table 4 and then filtered under vacuum. The filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (20:80). **5a**: Yield: 0.135 g (62%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.15 (d, 3.2 Hz, 1H), 6.94 (d, 3.2 Hz, 1H), 4.47 (s, 2H), 1.78–1.72 (m, 2H), 1.69 (qua, 7.4 Hz, 2H), 1.38 (s, 3H), 1.15 (t, 7.4 Hz, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 144.72, 142.45, 118.60, 118.44, 98.99, 87.51, 81.03, 68.48, 52.32, 35.65, 27.58, 11.00. MS m/z (%) 216 (13), 198 (33), 180 (100), 166 (31), 142 (17), 127 (17), 112 (11), 66 (61). IR (KBr, film) ν 3500–3100 (O–H), 3058, 2963, 2837, 1221, 1532, 1447, 1239, 858.