Synthesis of 2-Alkynyl-Tellurophene Derivatives via Palladium-Catalyzed Cross-Coupling

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Abstract: We present herein our results on the palladium-catalyzed cross-coupling of 2-halotellurophene with several terminal alkynes to give the 2-alkynyl-tellurophene derivatives in excellent yields. The reaction proceeded cleanly under mild conditions and was performed with propargyl alcohols, propargyl amines, propiolate, as well as alkyl and aryl alkynes, in the presence of $PdCl_2(PPh_3)_2$, Et_3N, THF and CuI.

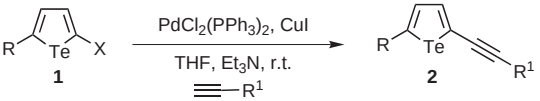
Key words: vinylic tellurides, palladium, cross-coupling, tellurophene, Sonogashira

Organochalcogenide compounds have been synthetic targets because of their effects on an extraordinary number of different reactions, including many carbon–carbon bond formations,[1] under relatively mild reaction conditions. Furthermore, organochalcogenides have become attractive synthetic targets because of their chemo-, regio- and stereoselective reactions[2] and their useful biological activities.[3]

Among organochalcogenides, the tellurophene derivatives play an important role in organic synthesis because of their excellent electrical properties, processibility, and environmental stability. However, studies on their chemistry are hampered by poor availability of this material.

Transition-metal-catalyzed cross-coupling reactions rank among the most important processes for constructing new carbon–carbon bonds. After 30 years, palladium-catalyzed coupling of terminal alkynes with the aryl halide, commonly referred as Sonogashira reactions,[4] a key stage in the synthesis of many currently interesting heterocycle-incorporated compounds,[5] continues to be one of the most powerful and attractive tools for $C(sp^2)$–C(sp) bond formation. By contrast, there are no reports on the use of halogenated tellurophenes as an electrophilic substrate for $C(sp^2)$–C(sp) bond formation using palladium cross-coupling reactions.

Herein, we report a new, efficient and mild palladium-catalyzed method to prepare 2-alkynyl tellurophene derivatives. We found that direct coupling of 2-halotellurophene **1** with terminal alkynes in the presence of $Pd(PPh_3)_2Cl_2$ as catalyst, with CuI as co-catalyst in THF and triethylamine



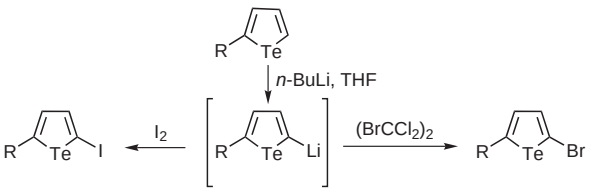
R = C_6H_5, C_4H_9; X = I, Br
R^1 = alkyl, aryl, propargyl amines, propargyl alcohols

Scheme 1

affords the desired 2-alkynyl tellurophene derivatives **2** in good yields (Scheme1).

The starting material required for the synthesis, 2-halotellurophenes **1**, was readily available by using the metallation of tellurophene[6] with *n*-butyllithium followed by the treatment of 2-(lithium)tellurophene **3** with iodine, leading the formation of 2-iodotellurophenes **1a**,**b**, isolated in 72% and 85% yields after purification.

In addition, 2-bromotellurophene **1c** was prepared via treatment of 2-(lithium)tellurophene **3** with 1,2-dibromo-1,1,2,2-tetrachloroethane, isolated in 88% yield (Scheme 2).[7]



1a R = C_4H_9 (85%)
1b R = Ph (72%)
1c R = C_4H_9 (88%)

Scheme 2

Our initial efforts were devoted to the selection of a suitable catalyst system for efficient Sonogashira coupling between 2-halotellurophene and terminal alkynes. Thus, 2-iodo-5-butyl-tellurophene (0.25 mmol) and propargyl alcohol (0.75 mmol) were treated in several solvents (2.5 mL) at room temperature with Pd(0) and Pd(II) catalysts, in the presence and absence of CuI and Et_3N (0.5 mL).

As shown in Table 1, both Pd(0) and Pd(II) catalysts tested did not exhibit catalytic activity when the reaction was carried out in the presence of pyrrolidine and diethylamine as solvent, even so using CuI as a co-catalyst and reflux temperature (Table 1, entries 1–5). However, when DMF, Et_3N, THF, MeCN, CH_2Cl_2, MeOH and hexane were used the coupled product was obtained in moderate to good yields either in the presence of Pd(0) or Pd(II)

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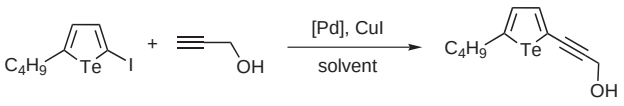
Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst (mol%)	Solvent	Yield (%)
1[b,d]	$Pd(PPh_3)_4$ (20)	Pyrrolidine	n.r.
2[d]	$Pd(PPh_3)_4$ (20)	Pyrrolidine	n.r.
3	$Pd(PPh_3)_4$ (20)	Pyrrolidine	n.r.
4[b]	$Pd(PPh_3)_2Cl_2$ (20)	Et_2NH	n.r.
5[c]	$Pd(PPh_3)_2Cl_2$ (20)	Et_2NH	n.r.
6[d]	$Pd(PPh_3)_2Cl_2$ (20)	DMF	64
7	$Pd(PPh_3)_2Cl_2$ (10)	DMF	73
8	$Pd(PPh_3)_4$ (20)	DMF	57
9	$Pd(PPh_3)_2Cl_2$ (10)	Et_3N	63
10	$Pd(PPh_3)_2Cl_2$ (10)	THF	71
11	$Pd(PPh_3)_2Cl_2$ (10)	MeCN	54
12	$Pd(PPh_3)_2Cl_2$ (10)	CH_2Cl_2	73
13	$Pd(PPh_3)_2Cl_2$ (10)	MeOH	71
14	$Pd(PPh_3)_2Cl_2$ (10)	Hexane	60

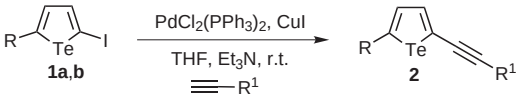
[a] Unless otherwise indicated, the reaction was carried out with Et_3N as base and CuI (10 mol%) as co-catalyst.
[b] The reaction was carried out in the absence of Et_3N.
[c] The reaction was carried out under reflux.
[d] The reaction was carried out in the absence of CuI.

catalyst (Table 1, entries 6–14). Thus, we chose $PdCl_2(PPh_3)_2$ (10 mol%), CuI (10 mol%), THF (2.5 mL), 2-iodo-tellurophene **1a** (0.25 mmol), propargyl alcohol **2a** (0.75 mmol) and Et_3N (0.5 mL) at room temperature for 12 hours, as the optimum condition for this coupling reaction.[8] In order to demonstrate the efficiency of this reaction, we explored the generality of our method extending the conditions to other terminal alkynes and the results are summarized in Table 2.

Concerning the structure of tellurophene, we found that neither 5-butyl- nor 5-phenyl-2-iodotellurophenes exhibited limitations in this methodology.

Inspection of Table 2 shows that the reaction worked well for a variety of propargylic alcohols. Both hindered and non-hindered propargyl alcohols gave the desired substituted tellurophene in good yields (Table 2, entries 1–6). When we performed this reaction with aryl alkynes, no differences were found between electron-withdrawing and electron-donating substituents (Table 2, entries 8–10). Our experiments also showed that the reaction with propargyl morpholynes gave similar yield to tertiary propargyl amines (Table 2, entries 12 and 13).

Table 2 2-Alkynyltellurophene **2** Prepared from 2-Iodotellurophene **1a**,**b** and Terminal Alkynes



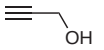
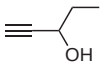
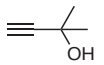
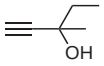
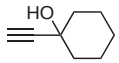
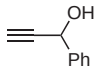
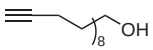
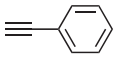
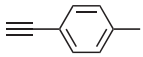
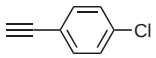
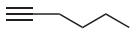
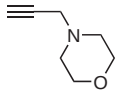
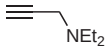
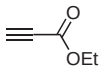
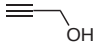
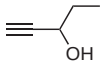
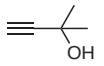
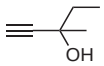
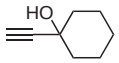
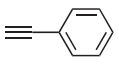
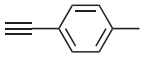
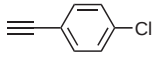
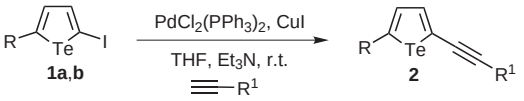
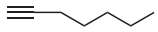
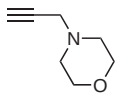
Entry	R	Alkynes	Yield (%)
1	C_4H_9 **1a**		71
2	**1a**		95
3	**1a**		84
4	**1a**		93
5	**1a**		95
6	**1a**		71
7	**1a**		97
8	**1a**		98
9	**1a**		96
10	**1a**		95
11	**1a**		80
12	**1a**		82
13	**1a**		81
14	**1a**		72
15	Ph **1b**		67
16	**1b**		94
17	**1b**		94
18	**1b**		95
19	**1b**		92
20	**1b**		70
21	**1b**		60
22	**1b**		69

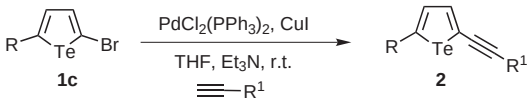
Table 2 2-Alkynyltellurophene **2** Prepared from 2-Iodotellurophene **1a**,**b** and Terminal Alkynes (continued)

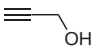
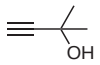
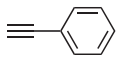
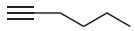
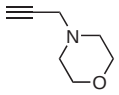


Entry	R	Alkynes	Yield (%)
23	**1b**		66
24	**1b**		92
25	**1b**		54

Having optimized the reaction conditions for 2-iodotellurophene we turned our attention to 2-bromotellurophene. Thus, we extended our standard catalytic system, used in the coupling reaction described in Table 2, to the reaction of 2-bromotellurophene **2** with terminal alkynes. These reactions produced the desired products in lower yields. We screened a representative range of terminal akynes, the results are shown in Table 3. The best results were obtained for propargyl alcohols and propargyl morpholyne (Table 3, entries 1, 2 and 5). Alkynyl and aryl alkynes gave the coupled products in moderate yields (Table 3, entries 3 and 4).

Table 3 2-Alkynyltellurophene **2** Prepared from 2-Bromotellurophene **1c** and Terminal Alkynes



Entry	R	Alkynes	Yield (%)
1	C_4H_9 **1c**		50
2	**1c**		66
3	**1c**		38
4	**1c**		43
5	**1c**		55

In summary, we have demonstrated that treatment of 2-halotellurophenes with terminal alkynes in THF in the presence of $Pd_2(PPh_3)_2Cl_2$/CuI (10 mol%) at room temperature results in the corresponding cross-coupled products in good yields. The cross-coupling reaction tolerates hindered and non-hindered propargyl alcohols, electron-withdrawing and electron-donating aryl alkynes, propargyl morpholyne, propargyl amine and alkyl alkynes. The biological activities of these compounds are under study in our laboratory. Analysis of the ^{1}H NMR and ^{13}C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.

Acknowledgment

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(8) **Typical Procedure for Cross-Coupling Reaction.**
A 25-mL, two-necked, round-bottom flask equipped with a magnetic stir bar and argon was charged sequentially with $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), THF (2.5 mL), 2-iodotellurophene (0.25 mmol), alkyne (0.75 mmol) and Et_3N (0.5 mL). The mixture was stirred at r.t. for 12 h. After this time, the mixture was filtered through a pad of alumina eluting with 50 mL of EtOAc. The organic phase was concentrated under vacuum and the residue was purified by flash chromatography.
Selected Spectral Data for 1-(5-Butyltellurophen-2-yl)pent-1-yn-3-ol.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, 1 H, *J* = 4.08 Hz), 7.17 (d, 1 H, *J* = 4.06 Hz), 4.5 (t, 1 H, 6.3 Hz), 2.84 (t, 2 H, 7.4 Hz), 2.30–2.15 (m, 1 H), 1.79 (quint, 2 H, *J* = 7.08 Hz), 1.60 (quint, 2 H, *J* = 7.8 Hz), 1.40 (sext, 2 H, *J* = 7.05), 1.03 (t, 3 H, *J* = 7.4 Hz), 0.92 (t, 3 H, *J* = 7.17 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.63, 142.05, 133.60, 118.87, 95.97, 85.07, 64.47, 36.66, 36.37, 22.03, 13.74, 9.46.