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New acetylenic furan derivatives: synthesis and anti-inflammatory activity

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Abstract—A series of acetylenic furan derivatives have been synthesized via Pd-catalyzed coupling reactions of 2-(alkyltelluro)furan with several terminal alkynes. These compounds showed good anti-inflammatory activity in the carrageenin-induced rat paw edema assay. This represents a new and efficient method for the synthesis of pharmacologically active compounds.

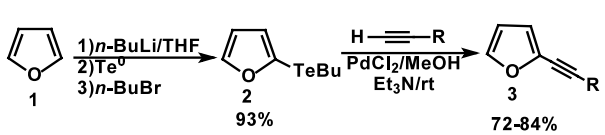
The benzofuran ring system is a commonly encountered heterocycle that is found in many natural products and synthetic drug molecules.[1] The biological profile of these agents is broad and depends on the nature and position of the substituents. For example, 5-methoxybenzofuran is a naturally occurring benzofuran with significant antibacterial properties, while 5-tetradecyloxy-2-acetylfuran is reported to be a potent inhibitor of rhinovirus.[1b,c,d] A plethora of other biological activities have been attributed to benzofurans, the best documented being their antioxidant and anti-inflammatory effects.[2]

Chemistry: palladium-catalyzed reactions with terminal acetylenes play an important role in organic synthesis.[3] The cross coupling of vinyl bromides, iodides, chlorides and triflates with monosubstituted acetylenes has been achieved in the presence of a Pd^0 or Pd^{II}/CuI catalyst using an amine as base.[4–8] The reaction has also been performed using bromoalkynes and vinyl metals, like vinyl boron,[9] copper,[10] zinc,[11] aluminum[12] or magnesium reagents.[13] The use of vinylic tellurides in cross coupling reactions has been previously described.[14] The reaction occurs smoothly with terminal alkynes leading to the corresponding enynes in good yields.[15]

Herein, we report a new, efficient and mild palladium-catalyzed method to prepare acetylenic furan derivatives and to determine their anti-inflammatory activity. We found that direct coupling of 2-(alkyltelluro)furan **2** with 1-alkynes in the presence of palladium dichloride as catalyst in methanol and triethylamine affords the desired acetylenic furan derivatives **3** in good yields (Scheme 1). The results of this exploratory study are summarized in Table 2.

The starting 2-(alkyltelluro)furan was readily available by using the metallation of furan **1** with *n*-butyllithium to give 2-furyllithium.[16] Treatment of 2-furyllithium with elemental tellurium followed by the addition of 1-bromobutane leads to the formation of the 2-(alkyltelluro)furan **2**, isolated in 93% yield after purification (Scheme 1).[17]

The experimental results indicated that cross coupling reaction of **2** with 1-alkynes in methanol as solvent in the presence of palladium(0) catalysts at room temperature for 48 or 24 h and using primary, secondary or tertiary amines such as $PrNH_2$, Et_2NH or Et_3N did not exhibit catalytic activity (Table 1, entries 4–6). The coupling reaction was also unsuccessful when using cyclic secondary amine with palladium(0) as catalysts (Table 1, entries 1–3).



Scheme 1.

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Table 1. Cross coupling reaction of **2** with 1-alkyne: Influence of palladium catalyst and amine

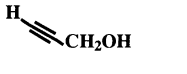
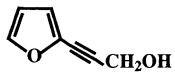
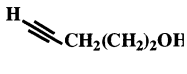
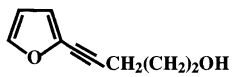
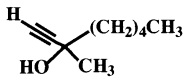
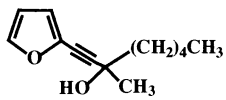
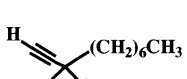
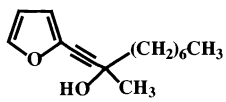
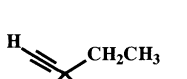
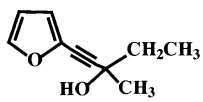
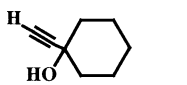
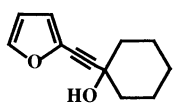
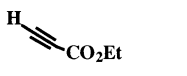
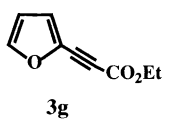
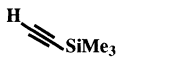
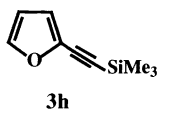
#	Catalyst (mol%)	Amine	Time (h)	Yield (%)
1	$Pd(PPh_3)_4$ (20)	Pyrrolidine	48	0
2	$Pd(PPh_3)_4$ (20)	Piperidine	48	0
3	$Pd(PPh_3)_4$ (20)	Morpholine	20	0
4	$Pd(PPh_3)_4$ (20)	Et_3N	20	0
5	$Pd(PPh_3)_4$ (20))	Et_2NH	24	0
6	$Pd(PPh_3)_4$ (20)	$PrNH_2$	20	0
7	$PdCl_2(PPh_3)_2$ (20)	Et_3N	24	12
8	$PdCl_2(PPh_3)_2$ (20)	Et_2NH	24	15
9	$PdCl_2(PPh_3)_2$ (20)	$PrNH_2$	24	8
10	$PdCl_2$ (20)	Et_3N	6	85

The best results were obtained when performing the reaction in the presence of palladium(II) catalysts and triethylamine as base (Table 1, entry 10). Under these conditions, the increase in the amount of $PdCl_2$ from 3 to 20% drastically improved the coupling reaction (20 to 85% yield). In our experiments the optimum condition for the coupling was found to be that using $PdCl_2$ (20 mol%), MeOH (5 mL), 2-(alkyltelluro)furan **2** (1 mmol), the appropriate 1-alkyne (2 mmol) and Et_3N (1 mmol) at 25°C for 6 h. By extending the coupling reaction to other alkynes, various acetylenic furan **3** were obtained in good yields[18] (Table 2). The formation of the enynes was confirmed by the analysis of the ^1H and ^{13}C NMR spectra.

Pharmacology: the obtained acetylenic furans **3a–c** were screened for anti-inflammatory activity using the carrageenin-induced paw edema method.[19] This rodent model of inflammation is customarily used for the screening of new pharmacologically active compounds and usually predicts whether a drug will have anti-inflammatory actions in humans.[20] The acetylenic furan **3c** (100 mg/kg; i.p) inhibited 40% of the edema ($p<0.05$ by Duncan's multiple range test), induced by carrageenin when compared to control (Fig. 1). Compound **3c** (250 mg/kg; i.p) inhibited paw edema formation with greater potency than acetylsalicylic acid (100 mg/kg, i.p),[21] a classical anti-inflammatory agent. Similarly, compound **3a** (250 mg/kg; i.p) prevented 50% of paw edema formation. However, acetylenic furan **3b** did not exhibit anti-inflammatory activity (at 100 and 250 mg/kg, i.p).

In conclusion, we have demonstrated that treatment of 2-(alkyltelluro)furan with 1-alkynes in methanol in the presence of $PdCl_2$ at room temperature results in the corresponding cross coupled products in high yields. The reaction proceeds clearly under mild conditions, and tolerates many sensitive functional groups, like alcohols, esters and silanes. The cross coupling reaction is sensitive to nature of the amine and catalyst. We have shown that $PdCl_2$ must be used instead of $PdCl_2$/CuI. Importantly, some acetylenic furans were pharmacologically active as anti-inflammatory agents in a reliable test.

Table 2. Acetylenic furan **3** prepared according to Scheme 1

#	1-alkynes	Acetylenic Furan **3**	Time (h)	Yield (%)
1		 **3a**	6	84
2		 **3b**	8	83
3		 **3c**	6	76
4		 **3d**	7	75
5		 **3e**	8	72
6		 **3f**	8	78
7		 **3g**	5	81
8		 **3h**	5	84

Acknowledgements

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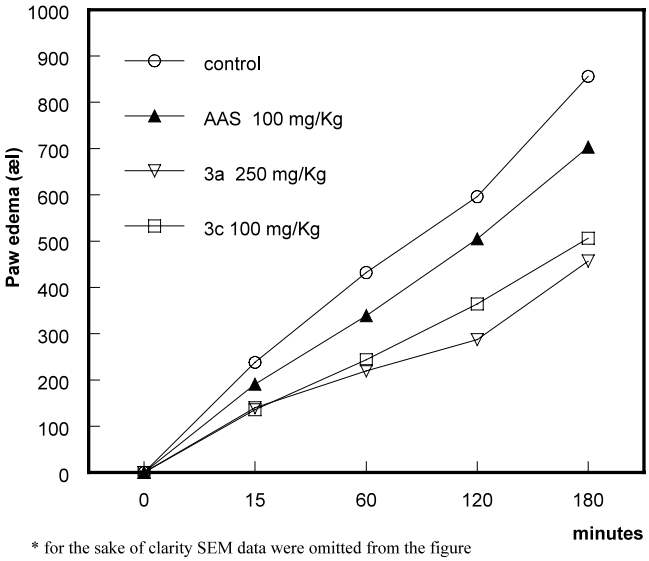

* for the sake of clarity SEM data were omitted from the figure

Figure 1.

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17. Procedure for the preparation of 2-(butyltelluro) furan **2**: To a two-necked round-bottomed flask under an argon atmosphere *n*-butyllithium (20 mmol, 1.5 M in hexane, 13.5 mL) was added dropwise to a solution of furan (20 mmol, 1.36 g) in freshly distilled dry THF (100 mL) at −78°C. The reaction mixture was then stirred for 30 minutes at this temperature and was allowed to warm to −40°C and elemental tellurium (20 mmol, 2.54 g) was added in one portion and the reaction was then stirred for an additional 1 h at this temperature. 1-Bromobutane (25 mmol, 3.43 g) was added at −10°C and the reaction mixture was stirred for 2 h at room temperature, quenched with saturated NH_4Cl (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** in 93%.
18. Typical procedure for **3b**: To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing $PdCl_2$ (0.035 g, 20 mmol) and dry methanol (5 mL) was added 2-(butyltelluro) furan **1** (0.252 g, 1 mmol). After stirring the mixture for 15 minutes at room temperature, 4-pentyn-1-ol (0.168 g, 2 mmol) and Et_3N (0.8 mL) were added. The reaction was stirred at room temperature for 8 h. After this time the solid part was filtered under vacuum and the filtrate was treated with saturated brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane/ethyl acetate (80:20). **Selected spectral and analytical data for 3b**: Yield 0.124 g (83%); ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm): 7.32 (dd, $J=0.6$, 1.8 Hz; 1H); 6.49 (dd, $J=1.8$, 3.4 Hz; 1H); 6.35 (dd, $J=1.8$, 3.4 Hz; 1H); 3.77 (t; $J=7.0$ Hz; 2H); 2.61 (t, $J=7.0$ Hz; 2H); 2.03 (s, 1H); 1.84 (qui, $J=7.0$ Hz; 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 142.69; 137.30; 113.76; 110.56; 93.77; 71.27. 61.25; 30.92; 15.85.
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21. **Bioassays**: Adult male rats were injected intraperitonially (1 ml/kg) with ethanol (control group) or with acetylenic furans dissolved in ethanol. After 1 h, carrageenin (0.01 mL, 2%) in physiological saline solution was injected in the plantar region of the right hindpaw. The volume of the injected paw was measured just before and 15, 60, 120 and 180 minutes after the injection of carrageenin. Measurements were done in triplicate for each animal. Data were analyzed by two-way analysis of variance (ANOVA) followed by Duncan's multiple range when appropriate. Experimenters were blind to the drug given to rats.