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Synthesis and anti-inflammatory activity of acetylenic thiophenes

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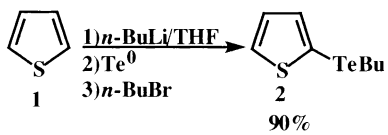
Abstract—A series of acetylenic thiophene derivatives have been synthesized via Pd-catalyzed coupling reaction of 2-(butyltelluro)thiophene with a variety of terminal alkynes. These compounds showed good anti-inflammatory activity in the carrageenin-induced paw edema assay on rats. © 2001 Elsevier Science Ltd. All rights reserved.

The concept of preparing thiophene analogs of biologically active benzenoids has stimulated researchers in pharmaceutical chemistry so that it now appears that at least one thiophene analog has been prepared for every important therapeutic compound containing a benzene nucleus. It was hoped that the thiophene analog would be as active as the parent compound or that the thiophene analog would, by virtue of its similar chemical structure, combine with the receptor, and, if not elicit a response of its own, serve effectively as a competitive inhibitor. Thus, when a thiophene analog is prepared, it is conceivable that such an agent may either intensify, mimic or antagonize the physiological activity of the parent substance.[1] Thiophene compounds are generally more toxic than their benzene analogs and, consequently, less effective medicinal agents. There are, however, some exceptions:[2] several thiophene derivatives have been found to show nematocidal,[3] insecticidal,[4] antibacterial,[5] antifungal[6] and antiviral[7] activity. In the present work, we describe the synthesis and anti-inflammatory activity of acetylenic thiophenes.

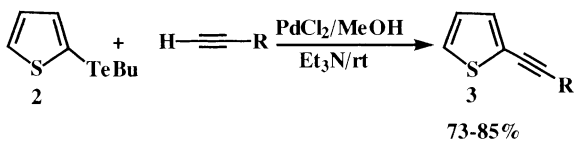
Chemistry: Palladium-catalyzed reactions with terminal acetylenes play an important role in organic synthesis.[8] The cross coupling of vinyl bromides, iodides, chlorides and triflates with monosubstituted acetylenes has been achieved in the presence of a Pd^0 or Pd^{II}/CuI catalyst using an amine as base.[9–13] The reaction has also been performed using bromoalkynes and vinyl metals, like vinyl boron,[14] copper,[15] zinc,[16] aluminum[17] or magnesium reagents.[18] The use of vinylic tellurides in cross coupling reactions has been previously described.[19] The reaction occurs smoothly with terminal alkynes leading to the corresponding enynes in good yields.[20]

In this communication we wish to report the preparation and the anti-inflammatory activity of acetylenic thiophenes. The starting material required by the synthesis, 2-(butyltelluro)thiophene **2**, was obtained from the metalation of thiophene **1** with *n*-butyllithium[21] followed by treatment of 2-thienyllithium with elemental tellurium. Subsequent addition of 1-bromobutane gave the 2-(butyltelluro)thiophene **2** in good yield (Scheme 1). This compound is stable and can be chromatographed and stored in the dark at room temperature for several days.

Treatment of 2-(butyltelluro) thiophene **2** with 1-alkynes in methanol using $PdCl_2$ as catalyst and triethylamine as base at room temperature gave the acetylenic thiophenes **3** in 73–85% yield after purification (Scheme 2).



Scheme 1.



Scheme 2.

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The cross coupling reaction of 2-(butyltelluro) thiophene **2** with 1-alkynes was very sensitive to the nature of the catalyst. Compound **2** (1 equiv.) was treated in methanol at room temperature with 2-propyn-1-ol (2 equiv.) in the presence of different palladium catalysts and Et_3N (1 equiv.) as base. As shown in Table 1, $Pd(PPh_3)_4$ or $Pd(PPh_3)_4$/CuI did not exhibit catalytic activity in this reaction (entries 1 and 2) and Pd (II) catalysts such as $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$ gave unsatisfactory yields of the desired enynes (entries 3–6). The reaction was greatly enhanced by using $PdCl_2$ from 3 to 10% (entries 7–10). However, by using $PdCl_2$ (10 mol%) the acetylenic thiophene **3a** was obtained in 85% isolated yield (entry 10).

The nature of the amine was also very important, because 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 (5–8%). However, by using Et_3N, the acetylenic thiophene **3a** was obtained in good yield. We also found that the yields of acetylenic thiophene were markedly decreased using DMF, CH_3CN, THF or CH_2Cl_2, instead of MeOH as the solvent. Thus, the optimum condition[22] for the coupling in Scheme 1 was found to be the use of $PdCl_2$ (10 mol%), MeOH (5 mL), 2-(alkyltelluro)thiophene **2** (1 mmol), the appropriate 1-alkyne (2 mmol) and Et_3N (1 mmol) at 25°C for 6 h. Moreover, the coupling reaction was extended to other alkynes. The results are summarized in Table 2.

The formation of the acetylenic thiophenes was confirmed by analysis of the ^1H and ^{13}C NMR spectra.

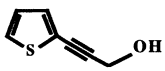
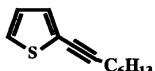
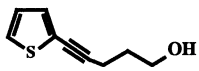
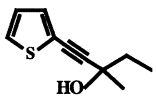
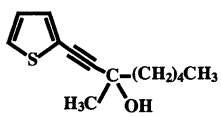
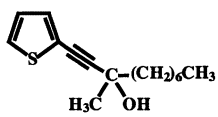
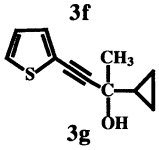
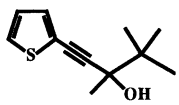
Pharmacology: The obtained acetylenic thiophenes **3a–c** were screened for anti-inflammatory activity using the carrageenin-induced paw edema method.[23] This method is customarily used for the screening of new pharmacologically active compounds. This rodent model of inflammation usually predicts whether a drug will have anti-inflammatory actions in humans.[24] The best results were obtained using the acetylenic thiophene **3c** (50% of the edema inhibition at a dose of 250 mg/kg; i.p.), demonstrating significant potential to reduce the carrageenin-paw edema when compared to acetylsalicylic acid (100 mg/kg, i.p, $P<0.05$).[25] In addition, compound **3c** exhibited a good curve-dose response (Fig. 1). However, acetylenic thiophenes **3a** and **3b** did not exhibit any activity (at 100 and 250 mg/kg, i.p). All acetylenic thiophenes are currently under study for other anti-inflammatory comportamental assay and antinociception activity and will be reported in due course.

In summary, the procedure described herein provides an interesting protocol for the synthesis of acetylenic thiophenes. We have shown that 2-(butyltelluro) thiophene **2** readily reacts with terminal alkynes at room temperature in MeOH in the presence of $PdCl_2$ to give the corresponding cross coupling products **3a–h** in high yields. The reaction proceeds smoothly and tolerates sensitive functional groups. The synthesized compounds also exhibited good anti-inflammatory activity and should be pharmacologically interesting.

Table 1. Influence of the ligands in the palladium complex

Entry	Catalyst (mol%)	Time (h)	Yield, **3d** (%)
1	$Pd(PPh_3)_4$/CuI (20)	48	0
2	$Pd(PPh_3)_4$ (20)	48	0
3	$PdCl_2/PPh_3$ (20)	20	12
4	$PdCl_2(PPh_3)_2$ (20)	20	15
5	$Pd(OAc)_2$ (20)	24	8
6	$PdCl_2(PhCN)_2$ (20)	20	10
7	$PdCl_2$ (3)	24	30
8	$PdCl_2$ (5)	24	47
9	$PdCl_2$/CuI (10)	6	72
10	$PdCl_2$ (10)	6	85

Table 2. Acetylenic thiophene **3** prepared according to Scheme 2

Entry	Acetylenic Thiophene **3**	Time (h)	Yield, (%)
1	 **3a**	6	85
2	 **3b**	8	82
3	 **3c**	5	80
4	 **3d**	5	83
5	 **3e**	7	75
6	 **3f**	4	79
7	 **3g**	7	73
8	 **3h**	8	82

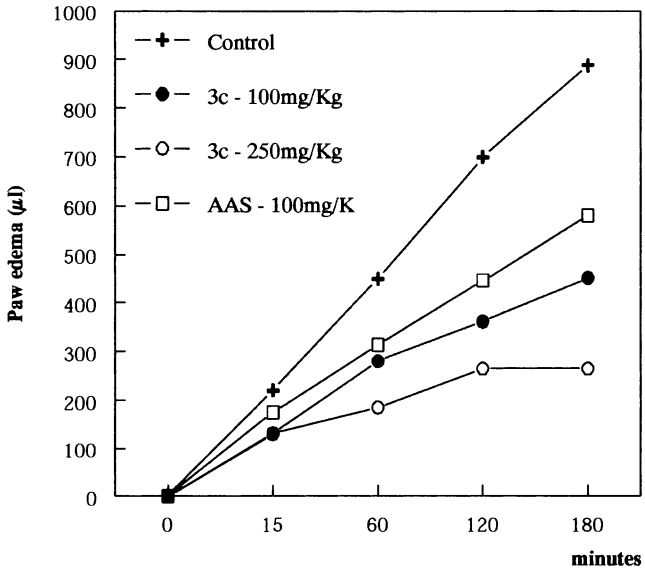


Figure 1.

Acknowledgements

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22. **Pd(II)-catalyzed cross-coupling reaction of 2-(butyltelluro) thiophene 2 with alkynes: general procedure**: To a solution of $PdCl_2$ (10 mol%, 0.018 g in MeOH (10 mL) at 25°C under an argon atmosphere, were added 2-(butyltelluro) thiophene **2** (1 mmol, 0.26 g), the appropriate alkyne (2 mmol) and Et_3N (0.8 mL). The mixture was stirred at room temperature for the time indicated in Table 1, treated with NH_4Cl saturated solution (5 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash silica-gel chromatography eluting with hexane (products **3b**) or hexane/ethyl acetate 7:3 (products **3a**, **3c**–**h**) to give the product **3**. **Selected spectral and analytical data for 3a**: Yield 0.11 g (85%); 200 MHz ^1H NMR ($CDCl_3$) $\delta = 7.36$–7.30 (m, 2H), 7.15–7.05 (m, 1H), 4.60 (s, 2H), 2.85 (s, 1H); 50 MHz ^{13}C NMR ($CDCl_3$) $\delta = 133.24$, 127.39, 126.93, 122.41, 91.11, 79.02, 51.67; IR (neat, cm^{-1}) ν 3367, 3102, 2221, 1416, 1356; LRMS (rel. int.) m/z 138 (100), 110 (55), 83(39), 45(64), 29(43).
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25. **Bioassays**: Wistar rats weighing 180–200 g were used for each group. Acetylenic thiophene compounds were injected intraperitoneally. After 1 h, carrageenin (0.01 mL, 2%) in physiological saline solution was subcutaneously injected under the plantar skin of the hind paw. The volume of the injected paw was measured just before and 15, 60, 120 and 180 min 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 test when necessary. The experimenter was blind to the drugs tested by using coded syringes.