An Easy Route to 2-(Z-Alkenyl)Thiophenes Via Sonogashira Coupling Followed by Stereoselective Alkyne Reduction

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A redução estereosseletiva da porção acetilênica do 2-(3-hidroxipropinil)tiofeno, levando ao correspondente derivado alcênico com estereoquímica *Z*, foi explorada utilizando-se uma variedade de reagentes e condições. O par ativado Zn(Cu), em metanol aquoso, exibiu os melhores resultados (88% de rendimento, *Z*:*E* = 98:2), embora o procedimento seja um tanto lento e laborioso. Resultados similares puderam ser obtidos mais facilmente utilizando-se o sistema Zn(Cu/Ag) ou o catalisador de Lindlar em atmosfera de hidrogênio, com uma moderada perda de estereosseletividade.

The stereoselective reduction of the alkyne moiety of 2-(3-hydroxypropynyl)thiophene, leading to the corresponding *Z*-alkenyl derivative, was explored using a range of reagents/conditions. Activated zinc-copper couple in aq. methanol proved to be the best combination (88% yield, *Z*:*E* = 98:2) although the procedure was rather slow and laborious. Similar yields could be obtained more straightforwardly using the Zn(Cu/Ag) reagent or H2/Lindlar catalyst with only a slight deterioration in stereoselectivity.

Key words: *2-iodo-5-lithiothiophene; acetylenic thiophenes; Z-alkenylthiophenes; stereoselective alkyne reduction.*

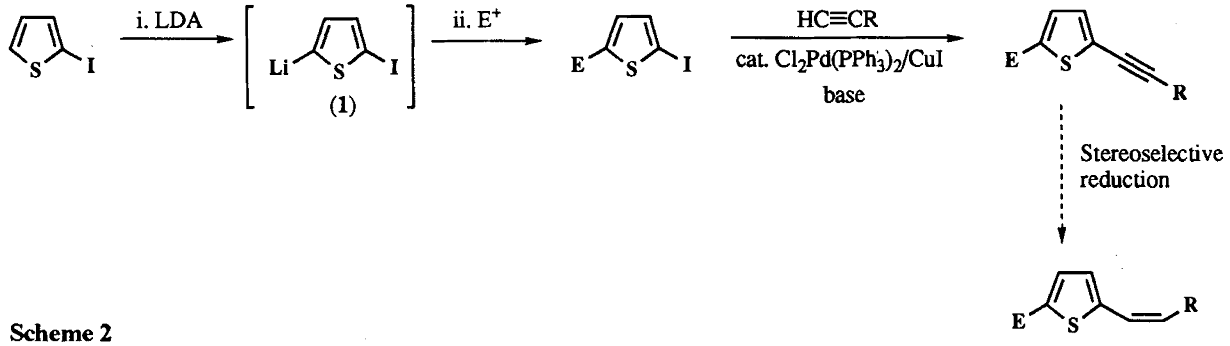
Introduction

The preparation of *Z*-alkenylthiophenes is not a trivial matter. The classical literature[1] describes a large number of procedures for the synthesis of substituted thiophenes but many of these are of very limited scope due to the harsh conditions normally employed. Alkynylthiophenes, however, are readily available, particularly with the discovery of the Sonogashira coupling reaction in which halothiophenes are coupled with terminal acetylenes under Cu(I)/Pd(0) catalysis.[2] In addition, we have recently shown that a wide variety of 2,5-disubstituted acetylenic thiophenes are available from 2-iodo-5-lithiothiophene (**1**) by electrophilic trapping followed by Sonogashira coupling[3] (Scheme 1). We were extremely interested in devising stereoselective procedures for the reduction of these acetylenic thiophenes to produce *Z*-alkenes as we felt that this sequence could provide the cornerstone for a short synthesis of novel sulphur-bridged Leukotriene analogues.[3-5] However, in view of the well known poisoning effect6 of thiophene on common hydrogenation catalysts (*e.g.* Ni, Pd, Pt) we envisaged that this transformation could prove to be problematic. In this paper, we compare a range of reduction procedures in terms of yield and stereoselectivity in order to determine the best methods for the conversion of acetylenic thiophenes into the corresponding Z-alkenyl derivatives. In a forthcoming paper5 the application of this methodology to leukotriene synthesis will be discussed.

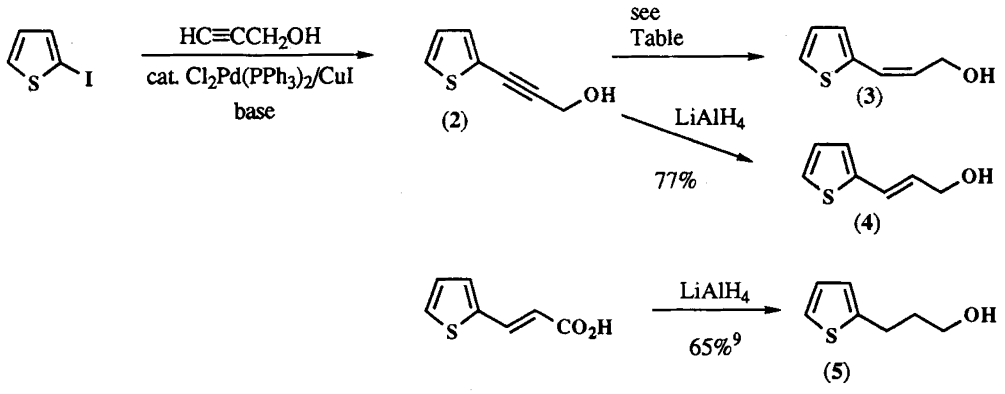
Method

The reduction studies were carried out on the model compound 2-(3-hydroxypropynyl)thiophene (**2**)[7] which was prepared by Sonogashira coupling of 2-iodothiophene and propargyl alcohol (Scheme 2). Likely by-products of the reduction reaction to give the (*Z*)-alkene (**3**) were also pre-

Scheme 1



Scheme 2



pared for comparison purposes: 2-[(*E*)-3-hydroxyprop-1-enyl]thiophene (**4**)[8] by the novel lithium aluminium hydride reduction of alkyne (**2**) and 2-(3-hydroxypropyl)thiophene[9] (**5**) by lithium aluminium hydride reduction of commercially available (*E*)-2'-thienylpropenoic acid as shown in Scheme 2.

The reduction studies are summarised in the Table. The reactions could be easily monitored by TLC, since the alkenes (**3**) and (**4**) and alkane (**5**) showed different colours to the starting material (**2**) when visualised with H_2SO_4 [**2**: red; **3** and **4**: blue; **5**: yellow]. The isomeric alkenes (**3**) and (**4**) were not separable on TLC analysis and the ratios were therefore determined by ^{1}H-NMR spectroscopy [**3**: δ 5.74, dt (*J* 11.9, 6.2 Hz), H-2' and δ 6.56, dt (J 11.9, 1.8 Hz), H-1'. **4**: δ 6.16, dt (J 16, 6 Hz), H-2' and δ 6.72, d (*J* 16 Hz), H-1']. The reduction methods described herein can be divided in three classes: (a) catalytic hydrogenations, (b) palladium mediated borohydride reductions and, (c) reductions performed using activated zinc.

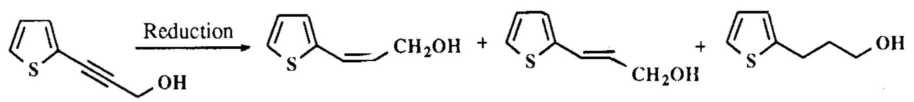
(a) Catalytic hydrogenations Surprisingly, hydrogenation[10] was not precluded by the presence of divalent sulphur in the heterocyclic ring[6] and the reductions proceeded readily even at atmospheric pressure. However, the *E*-isomer (**4**) and the over-reduced compound (**5**) were observed in all reactions. Attempts using 5% Pd-C gave mainly the over-reduced product (**5**) along with a mixture of unidentified by-products (Table, entry 1). We therefore investigated reactions using commercial Lindlar catalyst (entry 2). Initially, a relatively large amount of catalyst (2 g/mmol substrate) was employed, leading to a mixture of products consisting mainly of the over-reduced compound (**5**). After a number of variations were studied, it was found that the best results were obtained by the portion-wise addition of catalyst (200 mg/mmol substrate) as described in the experimental section. In this manner, a mixture of products consisting mainly of the required alkene (**3**) was obtained in 85-95% yields (*Z:E ca.* 97:3).

Brown *et al* reported[11] that alkyne semi-reductions could be carried out successfully using a hydrogenation catalyst known as P-2 nickel, formed from $NaBH_4$ and $Ni(OAc)_2$ (probably Ni_2B). However, catalyst poisoning appeared to be occurring when the reduction of (**2**) was attempted using this system and little conversion was observed, even after prolonged reaction times (entry 3).

(b) Palladium mediated borohydride reductions The use of a mixture of sodium borohydride, palladium(II) chloride and polyethyleneglycol (PEG) in dichloromethane has been reported[12] to give efficient *cis*-reduction of disubstituted alkynes, including phenylalkynes. In our hands, however, this procedure gave poor stereoselectivity (*Z:E ca.* 76:24). By carrying out the reaction with 2% $Pd(OAc)_2$ in ethanol without PEG (entry 4), stereoselectivity was improved (*Z:E ca.* 85:15) and the reaction was fast, high yielding, easy to perform and over-reduction was absent. Attempts to improve the stereoselectivity still further by the addition of ethylenediamine[11] were unsuccessful, this modification almost completely inhibiting the reduction (entry 5).

(c) Reductions performed by activated zinc. There have been several reports of alkynes being reduced to Z-alkenes using activated zinc powder.[13-16] The use of zinc powder activated with 1,2-dibromoethane (Zn-$C_2H_4Br_2$) (entry 6)[13] led only to the E-isomer (3) in 50% yield. The reagent

Table - Reduction of (2): Yields, stereoselectivity and reaction conditions.



(2) (3) (4) (5)

Entry	Reducing Agent	Solvent	T (ºC)	Time	Yield (%)	3 : 4: 5[c]	References
1	H_2/ 5% Pd-C	hexane-THF(10:1)	r.t.	1 h	a	0 : 0 : 100	10
2	H_2/Lindlar	hexane-THF(10:1)	r.t.	3 h	85 - 95	91 : 3 : 6	10
3	H_2/P2-Ni	EtOH	r.t.	24 h	b	a	11
4	Pd(II)/$NaBH_4$	EtOH	r.t.	3 h	70 - 80	85 : 15 : 0	12
5	Pd(II)/$NaBH_4$/EDA	EtOH	r.t.	11 days	b	a	12
6	Zn-$C_2H_4Br_2$	EtOH	reflux	17 h	50	0 : 100 : 0	13
7	Zn/Cu-$C_2H_4Br_2$	EtOH	40	1.5 h	0		13
8	Zn(Cu)-acid act.	MeOH	reflux	2 days	b	a	14
9	Zn(Cu)-base act.	aq. MeOH (1:14)	reflux	10 days	83 - 88	98 : 2 : 0	15
10	Zn(Cu/Ag)	aq. MeOH (1:1)	r.t.	1.5 h	82	92 : 8 : 0	16

a: Not determined.
b: TLC analysis showed very low conversion.
c: The ratio (3) : (4) : (5) was determined by ^{1}H NMR spectroscopy.

prepared from zinc powder successively activated with 1,2-dibromoethane, cuprous bromide and lithium bromide (Zn/Cu-$C_2H_4Br_2$) (entry 7)[13] and acid activated Zn(Cu) couple (entry 8)[14] were also investigated but little or no reduction was observed. However, very good results were obtained when a base-activated Zn(Cu) couple (prepared[15] by the addition of $CuCl_2$ to a Zn powder previously activated with KOH solution) was used. Thus, the desired alkenes (**3**) and (**4**) (*Z:E ca.* 98:2) were obtained in 83-88% yield after 10 days refluxing in MeOH-H_2O (14 : 1) (entry 9) without contamination by the over-reduced product (**5**). Another satisfactory result was obtained by the use of a Zn(Cu/Ag) reagent and again the over-reduced product (**5**) was absent (entry 10).[16] Although the stereoselectivity was not quite so high (*Z:E ca.* 92:8), the shorter reaction time and the milder conditions (1.5 h at room temperature) make this an attractive alternative.

In conclusion, of the several methods explored (see Table), the base-activated Zn(Cu) couple (entry 9) gives the best stereoselectivity. However, the vigorous conditions that have to be employed severely restrict the scope of this procedure. The Zn(Cu/Ag) reagent (entry 10) allows the reduction to be carried out in a short time and under much milder conditions although the stereoselectivity is slightly lower. Hydrogenation with a Lindlar catalyst (entry 2) gives similar yields and stereoselectivity to the Zn(Cu/Ag) procedure although over-reduction is also observed. These observations are of wider applicability as will be illustrated in a future publication.[5]

Representative Procedures. ^{1}H NMR spectra were recorded on a Jeol PMX 60 (60 MHz) or Jeol EX 90 (90 MHz) spectrometer. ^{13}C NMR spectra were recorded using a Jeol EX 90 (22.4 MHz) spectrometer. Infrared spectra (IR) were recorded using a Perkin-Elmer FT-IR 1720-X spectrometer. The liquid samples were deposited as thin films on sodium chloride plates and the solid samples were analysed as a nujol mull deposited on sodium chloride plates. Low resolution mass spectra (MS) were recorded on a Kratos MS 25. Lindlar catalyst and 5% Pd-C were purchased from the Aldrich Co. Thin layer chromatography (TLC) were performed on Merck 5554 aluminium-backed silica plates.

2-(3-Hydroxypropynyl)thiophene (**2**). Copper Iodide (0.30 g, 3 mol%) was added to a mixture of bis-(triphenylphosphine)palladium(II) chloride (1.12 g, 3 mol%), 2-iodothiophene (10.08 g, 0.048 mol) and propargyl alcohol (2.97 g, 0.053 mol) in freshly distilled, dry, triethylamine (145 mL) under a nitrogen atmosphere and 0 °C. The mixture was allowed to stir at room temperature until TLC showed that all of the starting material had disappeared (a period of 4 h was generally enough). The precipitate was then removed by filtration, washed with ether (3 x 5 mL) and the solvent was removed from the combined filtrates *in vacuo*. The crude brown oil was purified by Kugelrohr distillation to afford *2-(3-hydroxypropynyl)thiophene* (**2**) (5.64 g, 85%) as a yellow liquid; b.p. 130 °C / 0.5 mm Hg (lit.7 b.p. 82 °C / 0.03 mm Hg); Rf 0.23 (petrol - EtOAc, 2:1) which exhibited consistent spectroscopic and microanalytical data.

2-[(Z)-3-Hydroxyprop-1-enyl]thiophene (**3**). Method A: by reduction of alkyne (**2**) with base activated Zn(Cu) couple. Copper(II) chloride (1 g, 7 mmol) in H_2O (5 mL) was added to a Zn powder suspension (4 g, 61 mmol) in H_2O (5 mL) with vigorous stirring. The precipitate was washed twice with water (30 mL), activated with KOH solution (6 g, 100 mmol in 30 mL H_2O) for 30 min at 80 °C and washed until neutral. A mixture of methanol / water (60 mL, 14:1) was added to the catalyst prepared above, and the stirring was continued for 10 min. Compound (**2**) was added (1 g, 7 mmol) and the mixture was allowed to reflux for 10 days, when TLC (petrol-EtOAc, 2:1, H_2SO_4 to visualise) showed complete consumption of the starting material. The Zn(Cu) couple was removed by filtration and washed with ether (5 x 10 mL). The product was extracted from the MeOH / H_2O layer with ether (3 x 60 mL) and the ethereal fractions were combined, dried over $MgSO_4$, the solvent removed in vacuo. and the resulting solid recrystallised from Et_2O-petrol to afford *2-[(Z)-3-hydroxyprop-1-enyl]thiophene* (**3**) (0.86 g, 88%), as a yellow solid, m.p. 39.9 - 42.2 °C; R_f 0.22 (petrol - EtOAc, 2:1); (Found: C, 59.9; H, 5.8; S, 22.9. C_7H_8OS requires C, 59.97; H, 5.75; S, 22.73%); υmax 3226 (OH), 2924 (CH_2), 1620 (*cis* C=C) cm^{-1}; δH(90 MHz, $CDCl_3$, TMS) 2.51 (1 H, br s, exchangeable OH), 4.51 (2 H, dd, $J_{3,1}$ 1.8 Hz and $J_{3,2'}$ 11.9 Hz, H-3'), 5.74 (1 H, dt appears as quintet, $J_{2',1'}$ 11.9 Hz and $J_{2',3'}$ 6.2 Hz, H-2'), 6.56 (1 H, dt, $J_{1,3}$ 1.8 Hz and $J1,2'$ 6.2 Hz, H-1'), 6.91 - 7.04 (2 H, m, 3- and 4-Th.-H), 7.26 (1 H, dd, $J_{5,3}$ 1.5 Hz and $J_{5,4}$ 4.8 Hz, 5-Th.-H); δ_C (22.4 MHz, $CDCl_3$) 60.12 (C-3), 122.44, 126.11, 127.17, 127.89, 129.66, 139.52 (C-2, C-1 and 2- to 5-Th.-C); m/z 140 (M^+, 58%), 139 (9, M^+-H), 123 (12, M^+-OH), 97 (100, M^+-44).

Method B: by reduction of alkyne (**2**) with Zn(Cu/Ag). A zinc powder suspension (2.5 g, 38 mmol in 15 mL H_2O) was allowed to stir for 15 min under N_2, $Cu(OAc)_2.H_2O$ (0.28 g, 1.4 mmol) was added and the mixture stirred for 15 min before $AgNO_3$ (0.24 g, 1.4 mmol) was added and the exothermic reaction was allowed to stir for an additional 30 min period. The precipitate was filtered and carefully washed with H_2O (2 x 15 mL), MeOH (2 x 15 mL), acetone (2 x 15 mL) and Et_2O (2 x 15 mL). The Et_2O-moist Zn dust was immediately transferred into a mixture of MeOH / H_2O (10 mL, 1:1). The alkyne (**2**) (0.2 g, 1.45 mmol) in MeOH (2 mL) was added and the mixture was allowed to stir for a period of 1.5 h, before TLC showed complete consumption of (**2**). The title compound (**3**), (0.17 g, 82%), was obtained after filtration of the catalyst and removal of the solvent *in vacuo*. The spectral data were consistent with those presented above.

Method C: by hydrogenation of (**2**) in the presence of Lindlar catalyst. Compound (**2**) (215 mg, 1.56 mmol) was dissolved hexane-THF (10 mL, 10:1) and Lindlar catalyst (200 mg) was added to the mixture. The flask was purged with H_2, attached to a balloon filled with hydrogen, and the mixture was allowed to stir for 1.5 h before TLC (petrol-EtOAc, 3:1, H_2SO_4 to visualise) still showed the red starting material spot. An additional amount of catalyst (100 mg) was then added and stirring continued for one more hour under a hydrogen atmosphere. A final portion of catalyst (50 mg) was added, as TLC indicated the continued presence of starting material. Work-up was performed after 30 min of the last catalyst addition (when only the blue product spot could be observed by TLC) simply by filtration of the catalyst and removal the solvent *in vacuo*, to afford the Z-alkene (**3**) (201 mg, 92%). The spectral data obtained for this compound were consistent with those presented above.

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