Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7785-7788, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01819-4

Synthesis of Polysubstituted Thiophenes by a Catalytic Cyclisation of Functionalised Episulfides

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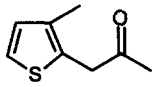
Abstract: Substituted thiophenes are formed by the reaction of 1-alkynyl-2,3-epithioalcohols with a catalytic amount of mercury^{II} prepared from HgO and dilute sulfuric acid. © 1997 Elsevier Science Ltd.

Compounds containing a thiophene ring provide unabated interest in terms of pharmacology,[1a] synthesis[1b] and reactivity.[1,2] For example thiophene **1** is a flavouring agent[3] and thienylethanolamines including **2**, R = 2-(3,4-dimethoxyphenylethyl), display significant antihypertensive activity.[4] Anticancer properties are exhibited by an analogue of retinoic acid that incorporates a tetrasubstituted thiophene ring.[5] Antihistamine activity in isolated guinea pig ileum has been noted for some β-thienyl-α,β-unsaturated carbonyl compounds.[6] The synthetic versatility of thiophenes is illustrated in their reduction to tetrahydrothiophenes by ionic hydrogenation[7] and their cleavage with Raney nickel to give carbon frameworks otherwise only accessible with difficulty.[8]



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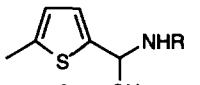
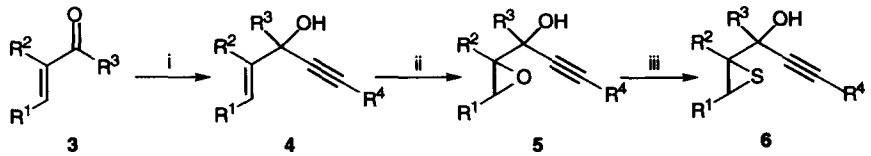


2

Recently, we showed that 1-alkynyl-2,3-epoxy alcohols undergo rearrangement to substituted furans upon treatment with a catalytic amount of Hg^{II} in very dilute sulfuric acid at 20 °C.[9] We now report a new related transformation of episulfides that provides a versatile route to a wide variety of substituted thiophenes.

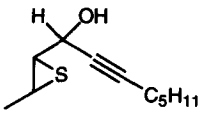
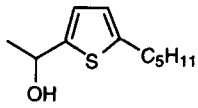
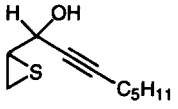
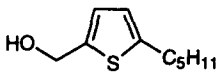
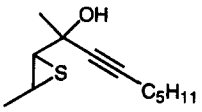
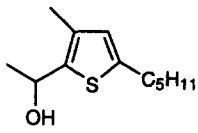
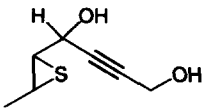
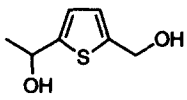
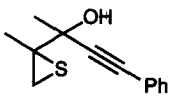
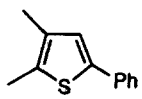
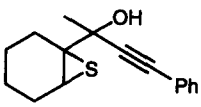
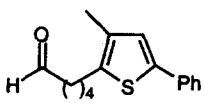


3 **4** **5** **6**

Scheme 1: Reagents: i, $R^4C{\equiv}CH$, BuLi ii, *t*-BuOOH and $VO(acac)_2$; or *m*-CPBA iii, thiourea, H_2SO_4.

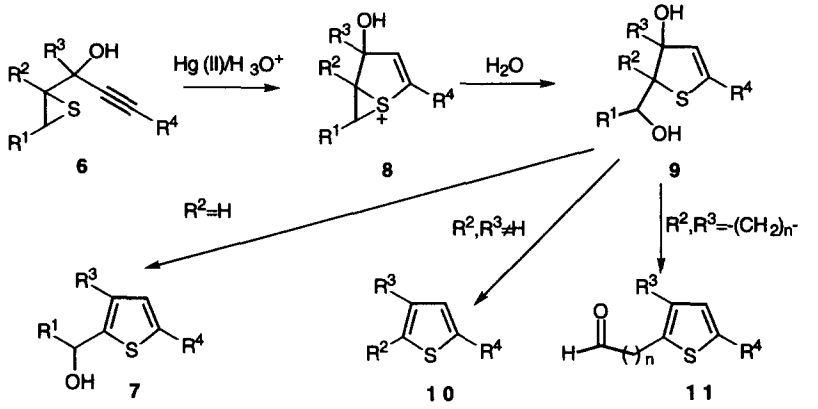
Reaction of an α,β-unsaturated carbonyl compound **3** with an alkynyllithium (generated by addition of 1.3 equiv. of BuLi to the alkyne at 0 °C) afforded the enynol **4**, which was epoxidised[10] using $Bu^tOOH/VO(acac)_2$ or *m*-CPBA to give a mixture of *syn*- and *anti*-epoxyalcohols **5**. Reaction of the epoxyalcohols **5** with thiourea/H_2SO_4[11] smoothly gave the corresponding episulfides at 20 °C (unoptimised yields of 55-70%). Thus, **4c** (formed from

Table: Mercury[II] Catalysed Conversion of Episulfides into Thiophenes

Episulfide	*Syn* : *Anti*	Thiophene	Yield (%)
 **6a**	1:1	 **7a**	72
 **6b**	5:6	 **7b**	80
 **6c**	4:5	 **7c**	70
 **6d**	1:2	 **7d**	66
 **6e**	1:6	 **10a**	63
 **6f**	1:4	 **11a**	70

the enone **3c** in 86%) was epoxidised to give **5c** (60%) and the latter converted into **6c** (70%). Treatment of a variety of substituted episulfides **6** with Hg^{II}/H_2SO_4[12] afforded thiophenes (Table). In the examples investigated, no evidence was obtained to suggest that the yields of the thiophene depend upon the ratio of episulfide diastereoisomers. The same procedure[11] carried out on **6a** without the addition of HgO gave no thiophene, and only **6a** was recovered. Other metals were tested, but no reaction of episulfides **6** was observed when HgO was replaced by $NiCl_2$, $Cu(OAc)_2$ or $ZnCl_2$.

The formation of the thiophenes can be rationalised by invoking a common intermediate of the type **9**. Thiophenes **7a-7d** would then arise by dehydration of **9** (R^2=H). For the episulfides **6e** and **6f**, direct dehydration of the intermediate **9** ($R^2 \neq H$) is blocked, and alternative pathways involving cleavage to carbonyl moieties occur. Thus, episulfide **6f** undergoes cleavage to **11a** containing an aliphatic aldehydic linkage, whereas **6e** fragments with loss of methanal to give thiophene **10a**. Initial formation of a mercurinium ion is presumed, and subsequent formation of an organomercurial intermediate, particularly involving a bond to the (formerly alkynic) carbon atom adjacent to the carbinol carbon atom cannot be excluded. Although no direct evidence for an episulfonium ion **8** is available, related episulfonium ions allow rationalisation of the attack of a variety of nucleophiles on simple *S*-heterocycles[13] as well as thiosugars.[14]



Scheme 2: Pathways to Polysubstituted Thiophenes

The new methodology offers a rational, predictable route to thiophenes bearing substituents either with no functionality, or with one or two oxygenated units. Of particular note is the conversion of the hydroxymethyl substituted alkyne unit of **6d** into the unsymmetrical diol **7d**. The oxygen atom that becomes incorporated into the furan products described in our previous communication[9] was not identified. However, this study shows unambiguously that efficient incorporation of the heteroatom in the three-membered ring

occurs, at least in cases of thiophene formation. The mechanism of this new regiocontrolled route to thiophenes and its synthetic applications are currently under investigation.

Acknowledgment. We are grateful to the Engineering and Physical Sciences Research Council for a Quota award (to J.C.).

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12. All compounds gave satisfactory spectral data (^{1}H and ^{13}C NMR, IR and MS), and all new compounds gave satisfactory analytical data or HRMS. The procedure is described for **7a**: a solution of **6a** (83 mg, 0.42 mmol) in acetone (20 mL, HPLC grade) was treated with a 0.1M aqueous solution (0.25 mL) of mercury^{II}, obtained by adding solid HgO to 2.5% (v/v) H_2SO_4. The mixture was stirred for 1 h and neutralised by addition of solid sodium hydrogen carbonate. Filtration and concentration *in vacuo* afforded an oil to which water (5 mL) and diethyl ether (10 mL) were added. Extraction with ether (2 x 15 mL) and chromatography (silica; petroleum ether: ethyl acetate, 9:1) afforded thiophene **7a** (60 mg, 72%) as a colourless oil. Only for **6f** were different concentrations of mercury^{II} (0.2 M) and sulfuric acid (5%) used.
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(*Received in UK* 22 *August* 1997; *accepted* 29 *August* 1997)