Tetrahedron Letters,Vol.26,No.16,pp 1983-1984,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

GENERAL SYNTHESIS OF POLYSUBSTITUTED THIOPHENES FROM DIKETO SULFIDES

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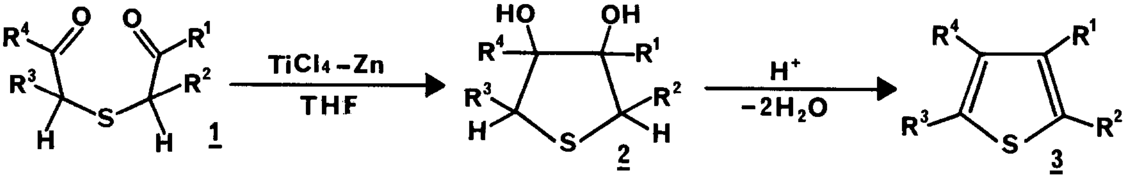
Abstract: Treatment of diketo sulfides with a low-valent titanium reagent at 0 °C (in two cases at room temperature) affords 3,4-dihydroxythiolanes in good yields. The acid-catalyzed (*p*-toluenesulfonic acid) dehydration of the latter compounds leads to the corresponding thiophenes in excellent yields.

Thiophenes, one of the most fundamental heterocycles, are important intermediates in organic synthesis[1] and their synthetic study continues to attract much attention. Although monosubstituted thiophenes are relatively easily derived from thiophene, preparation of polysubstituted thiophenes is much more difficult.[2] We reported that 2,5-dihydrothiophenes are prepared from diketo sulfides (**1**) by an intramolecular reductive coupling reaction using a low-valent titanium reagent prepared from titanium(IV) chloride and zinc powder.[3] Herein we report that this reductive coupling reaction, when carried out at lower temperatures and quenched at the early stages of the reaction, affords 3,4-dihydroxythiolanes (**2**) in good yields[4] and that the acid-catalyzed dehydration of **2** leads to thiophenes (**3**) in excellent yields, thus providing an efficient general synthesis of polysubstituted thiophenes which starts from easily accessible compounds.[5,6]

Table 1 summarizes the preparation of polysubstituted thiophenes **3** from diketo sulfides **1** by this method.

The intramolecular reductive coupling reaction in entries 1-4 affords the corresponding cis-diols exclusively.[7] The cis geometry was determined by spectroscopic methods and chemical transformations. For example, the oxidation of 3,4-diphenyl-2,5-dihydrothiophene (**5**)[3] with m-CPBA and then with osmium tetraoxide gives *cis*-3,4-dihydroxy-3,4-diphenylthiolane 1,1-dioxide (**6**) in a good yield. The same compound was quantitatively derived from the the 3,4-dihydroxythiolane **4** (the product in entry 1) by oxidation with m-CPBA.[8] In entry 5, when pure meso-sulfide was subjected to the reduction, the sole cis-isomer was selectively formed. In other cases (entries 8-12) diketo sulfides used are mixtures of erythro- and threo-isomers (meso and d,l), and hence diols **2** were obtained as stereoisomeric mixtures and subjected to dehydration as they were.

The dehydration was readily accomplished by refluxing a solution of **2** in toluene for



1 h in the presence of a catalytic amount of *p*-toluenesulfonic acid ($BF_3 \cdot Et_2O$ was used with one case). No products due to pinacol rearrangement were formed.

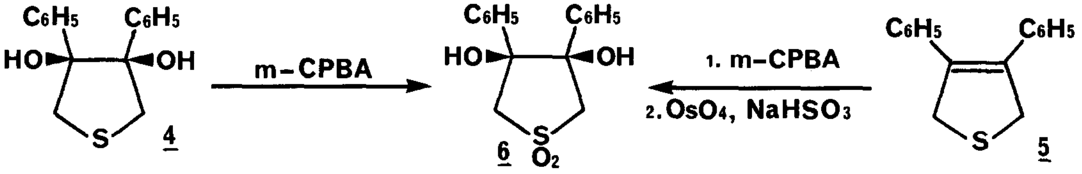
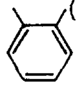


Table 1 Preparation of Thiophenes (3) from Diketo Sulfides (1) via Dihydroxythiolanes (2)

entry	R^1	R^2	R^3	R^4	yield (%, 1 $\rightarrow$ 2)$^{a)}$	yield (%, 2 $\rightarrow$ 3)
1	C_6H_5	H	H	C_6H_5	82	98
2	4-BrC_6H_4	H	H	4-BrC_6H_4	84	93
3	4-MeC_6H_4	H	H	4-MeC_6H_4	78	95
4	2-naphthyl	H	H	2-naphthyl	71	98
5	C_6H_5	CH_3	CH_3	C_6H_5	82	92
6	C_6H_5	C_2H_5	C_2H_5	C_6H_5	93	93
7	C_6H_5	H	CH_3	CH_3	73	93
8	C_6H_5	CH_3	CH_3	CH_3	75	89
9	C_6H_5	C_6H_5	CH_3	CH_3	71	89
10	CH_3	CH_3	CH_3	CH_3	71$^{b)}$	73$^{c)}$
11	$-(CH_2)_4-$		CH_3	CH_3	50$^{b)}$	92
12	 $(CH_2)_2$-		CH_3	CH_3	73	85

a) Unless otherwise stated, the mixture was stirred at 0 °C for 1-3 h.

b) Room temperature for 3 h.

c) The dehydration was accomplished by using $BF_3 \cdot Et_2O$ in refluxing methylene chloride.

References and Notes

1. A. I. Meyers, "Heterocycles in Organic Synthesis," John Wiley, New York, 1973.
2. (a) D. E. Wolf and K. Folkers, "Organic Reactions," John Wiley, New York, 1951, Vol. 6, p. 410. (b) G. R. Newkome and W. W. Paulder, "Contemporary Heterocyclic Chemistry," John Wiley, New York, 1982.
3. J. Nakayama, H. Machida, and M. Hoshino, Tetrahedron Lett., preceding paper in this issue.
4. The following is a typical procedure of the conversion of 1 to 2. To a stirred and cooled (ca. -10 °C) solution of 2.70 g (10 mmol) of diphenacyl sulfide in 80 mL of THF was added 5.0 mL (45 mmol) of titanium(IV) chloride and then 6.0 g (90 mg. atoms) of zinc powder in small portions. The mixture was stirred for 15 min, warmed to 0 °C, and stirred for 1 h at this temperature. The resulting mixture was quenched with 10% aqueous potassium carbonate. Methylene chloride (200 mL) was added to the mixture and the two-phase mixture was filtered through celite. The methylene chloride layer was washed with water, dried, and evaporated. The resulting crude product was purified by silica gel column chromatography to give 2.23 g (82%) of *cis*-3,4-dihydroxy-3,4-diphenylthiolane (entry 1).
5. This work was supported in part by the Grant-in-Aid (No. 5940298) from the Ministry of Education, Culture and Science, Japan.
6. Although thiophenes 3 can be prepared from 2,5-dihydrothiophenes (ref. 3) by oxidation with DDQ, the present method is more economical and simple.
7. The reduction of 1,2-diacetylethane by the low-valent titanium reagent prepared from titanium(IV) chloride and Mg-Hg gives *cis*-1,2-dihydroxy-1,2-dimethylcyclobutane: E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, J. Org. Chem., 41, 260 (1976).
8. Additional evidence comes from its conversion to *meso*-2,3-dihydroxy-2,3-diphenylbutane by reduction with Raney nickel (W-2). Preparation of meso-diols by this procedure will be described elsewhere.

(Received in Japan 10 January 1985)