A Simple Synthesis of 7-*t*-Butyl-4-methyl-2,3-dihydrothiepin

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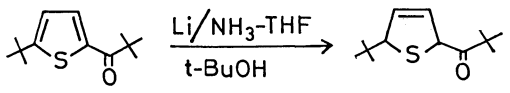
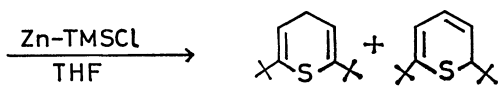
Synopsis The novel ring expansion reaction developed for the synthesis of 2,6-di-*t*-butylthiopyrans has been applied to the short path preparation of a dihydrothiepin derivative. Thus, 4-methyl-6-pivaloyl-3,6-dihydro-2*H*-thiopyran was converted into 7-*t*-butyl-4-methyl-2,3-dihydrothiepin in excellent yield by using chlorotrimethylsilane-zinc reagent in tetrahydrofuran.

Strategies for the synthesis of organic compounds using silicon-based reagents have been developed extensively, and their utility has been well documented.[1] However, one of these, chlorotrimethylsilane-zinc (or zinc amalgam) reagent induces formation of double bonds directly from ketones under mild conditions.[2] It provides some novel synthetic methods,[3] but has received little attention although it appears to occupy a prominent place in organic synthesis. In connection with our efforts directed toward the synthesis of stable monocyclic thiepins[4] we have recently demonstrated the novel and versatile synthesis of 2,6-di-*t*-butylthiopyrans from the corresponding acyldihydrothiophene using this reagent (see Scheme 1). Otherwise this substance is difficult to make.

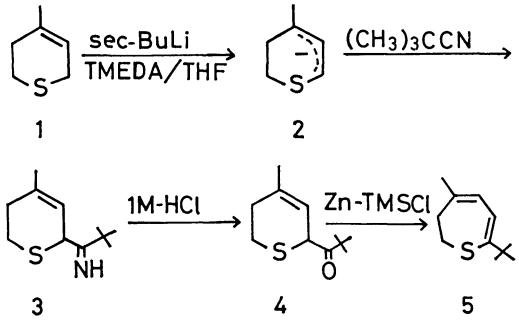
This method appears to have promise as a tool for the synthesis of seven membered rings containing a sulfur atom such as thiepin derivatives directly from appropriate six-membered precursors. In this context, the synthesis of 7-*t*-butyl-4-methyl-2,3-dihydrothiepin (**5**) starting from readily available **1**[5] was examined (Scheme 2).

The desired precursor **4** was prepared starting from **1**; the anion **2**[5,6] generated from **1** with s-butyllithium in THF in the presence of TMEDA at −78 °C was treated with pivalonitrile at −20 °C to give exclusively the crude imine **3** in high yield. Hydrolysis of **3** with 1 M (1 M=1 mol dm^{-3}) hydrochloric acid in THF–water formed **4**, whose structure was characterized unequivocally by a combination of elemental analysis and spectral data (^{1}H NMR, IR, and high resolution mass spectrum). It is interesting to note that the ambident anion **2** reacts exclusively at α-carbon of the sulfur atom with pivalonitrile.





Scheme 1.



Scheme 2.

The acylthiopyran **4** thus obtained led to the final product, dihydrothiepin (**5**) in excellent yield by treatment with chlorotrimethylsilane and activated zinc powder in THF at 0 °C. It was purified by column chromatography on alumina and elution with hexane. Its structure was confirmed by a full range of spectral data (see experimental section).

The successful conversion of **4** into **5** provides a new methodology for ring expansion reactions of sulfur heterocycles. Numerous applications will undoubtedly follow.

Experimental

^{1}H NMR (100 MHz) spectra were recorded on a Varian XL-100 spectrometer with TMS as the internal standard, IR spectra were recorded on a JASCO A-100 instrument, and mass spectra were obtained on a JEOL JMS-01SG-2 spectrometer.

*4-Methyl-6-pivaloyl-3,6-dihydro-2*H*-thiopyran (4).* To a solution of thiopyran (**1**; 0.31 g, 2.7 mmol) in 6 ml of tetrahydrofuran in the presence of 0.40 ml of TMEDA, was added 5.0 ml of 0.54 M s-butyllithium in hexane at −50 °C. After the solution was allowed to warm to −20 °C for 1 h, 0.28 ml (2.5 mmol) of pivalonitrile was added to the solution cooled to −50 °C with stirring, and the reaction mixture was stirred for an additional 3 h at −20 °C. After addition of water, the product was extracted with ether, and the ether solution dried over anhydrous sodium sulfate. Removal of the solvent gave the crude imine **3**; yield: 0.47 g (88.5%). IR (neat: ν=1620 cm^{-1}. ^{1}H NMR (CCl_4): δ=1.17 (s, 9H); 1.77 (s, 3H); 2.28 (m, 2H); 2.57 (m, 2H), 3.90 (d-like, 1H); 5.17 ppm (m, 1H). To 0.34 g (1.7 mmol) of crude imine **3** in 7 ml of THF was added 2 ml of 1 M hydrochloric acid at room temperature, the reaction mixture was stirred for 3 h. The product was extracted with hexane and the combined extracts dried over anhydrous sodium sulfate. Removal of the solvent gave crude acylthiopyran **4**, which was purified by short column chromatography (alumina) and elution with benzene to give pure **4**; yield: 0.336 g (98%). IR (neat): ν=1695 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ=1.23 (s, 9H); 1.76 (bs, 3H); 2.22—3.00 (m, 4H); 4.30 (d, 1H, J=6.0 Hz); 5.33 ppm (m, 1H). Found: C, 66.95; H, 9.23; S, 15.72%. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.15; S, 16.17%. High Mass m/e=198.1070 (Calcd for $C_{11}H_{18}OS$; 198.1077).

7-t-Butyl-4-methyl-2,3-dihydrothiepin (5). To a suspension of 1.68 g of activated zinc powder in the solution of **4** (0.30 g, 1.5 mmol) in 15 ml of THF, 3.2 ml (25 mmol) of chlorotrimethylsilane was added dropwise at 0 °C with

stirring over 3 h. To the reaction mixture cooled to −20 °C, 1 ml of 1 M sodium hydroxide solution was added carefully. After removal of the zinc by decantation, the product was extracted with hexane, and the extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave **5**, which was distilled at 50 °C/4 Torr. Yield: 270 mg (99%). ^{1}H NMR ($CDCl_3$): δ=1.16 (s, 9H); 1.86 (s, 3H); 2.66 (t-like, 2H); 2.87 (t, 2H, J=5.0 Hz); 5.73 (m, 1H); 5.87 ppm (d, 1H, J=8.0 Hz). Found: C, 72.56; H, 9.95; S, 17.36%. Calcd for $C_{11}H_{18}S$: C, 72.47; H, 9.95; S, 17.58. High Mass m/e=182.1122 (Calcd for $C_{11}H_{18}S$; 182.1127).

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