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A ROLE OF 2,7-DIISOPROPYL GROUPS IN THE STABILITY OF THIEPIN1)

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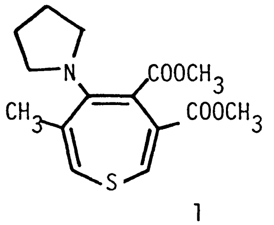
2,6-Diisopropyl-4-methylthiopyrylium tetrafluoroborate (18) was converted into the diazoester (19) by reaction with ethyl lithiodiazoacetate. Treatment of 19 with Pd(II) complex resulted in exclusive formation of ethyl 4,5-diisopropyl-2-methylbenzoate (21) through sulfur extrusion of the intermediate thiepin (20) even at -70°C.

Unlike 1H-azepines2) and oxepins3), thiepins4) are known to convert easily into corresponding benzenoid compounds by valence isomerization of the thiepin to the thianorcaradiene valence isomer followed by irreversible loss of sulfur. From some recent reports, it has become apparent that the stability of a thiepin ring system can be enhanced by either electronic or steric effect of suitable substituents. Typical examples of thiepins stabilized by either of these two ways are 3,4-di(methoxycarbonyl)-6-methyl-5-pyrrolidinothiepin (1)5) and the tetracyclic thiepin (2),6) respectively.



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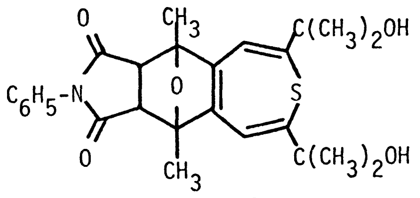

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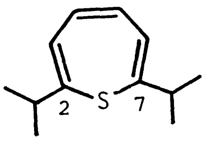

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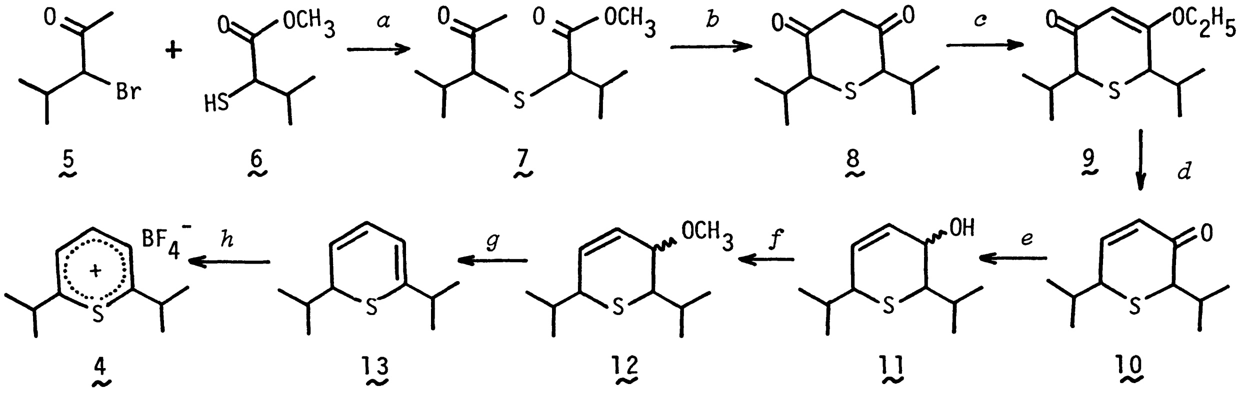
The present study is based on the finding that the unusual thermal stability of 2 may originate from the presence of two bulky groups at 2- and 7-positions of the thiepin ring.6) Thus, our hope was to synthesize a monocyclic thiepin with sterically bulky group such as (3) under mild catalytic conditions.

Scheme-17) outlines the synthetic sequence of 2,6-diisopropylthiopyrylium tetrafluoroborate (4), a key intermediate of our thiepin synthesis,1) starting from 3-bromo-4-methylpentan-2-one (5)8) and methyl 2-mercapto-3-methylbutyroate (6).9) The tetrafluoroborate of the cation 47) was formed as stable white crystals of mp 80°C [IR, ν=1050 cm^{-1} (BF_4^-); UV, λ_{max} (CH_3CN)=247 nm (log ε 3.61), 308 (3.92); ^{1}H-NMR, δ(CF_3COOH)=1.63 (12H, d, J=7.0 Hz), 3.80 (2H, sept, J=7.0 Hz), 8.55 (2H, A-part of A_2B, J_{AB}=8.7 Hz), 8.85 (1H, B-part of A_2B)].

Reaction of 4 with ethyl lithiodiazoacetate11) in a 3:1 mixture of tetrahydrofuran and ether at -120~-110°C furnishes a single diazo compound (14) in 94% yield. The structure of 14 was established by its IR [ν=2050, 1670 cm^{-1}] and

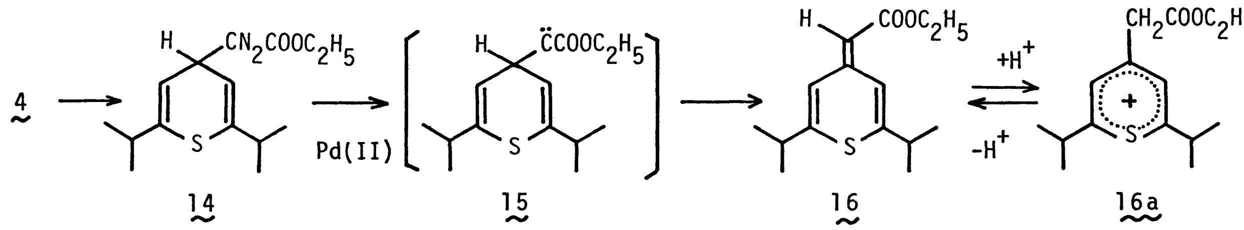
[scheme - 1]



a: $NaOCH_3/CH_3OH$ (100%), b: $NaOCH_3/CH_3OH$/benzene, room temp. for a day (96%), c: p-$CH_3C_6H_4SO_3H/C_2H_5OH$/benzene, reflux for 7.5 h (73%), d: $LiAlH_4$/ether, gentle reflux for a day (74%), e: $LiAlH_4$-$AlCl_3$/ether, room temp. for 10 min, f: NaH/THF, room temp, for 2.5 h; CH_3I, room temp. for 35 min; 50°C for 5 min (70%), g : LiN(i-Pr)$_2$/ether, -73°C for 2.5 h (82%), h: Ph_3C^+ BF_4^-/CH_3CN, 22°C, (94%).

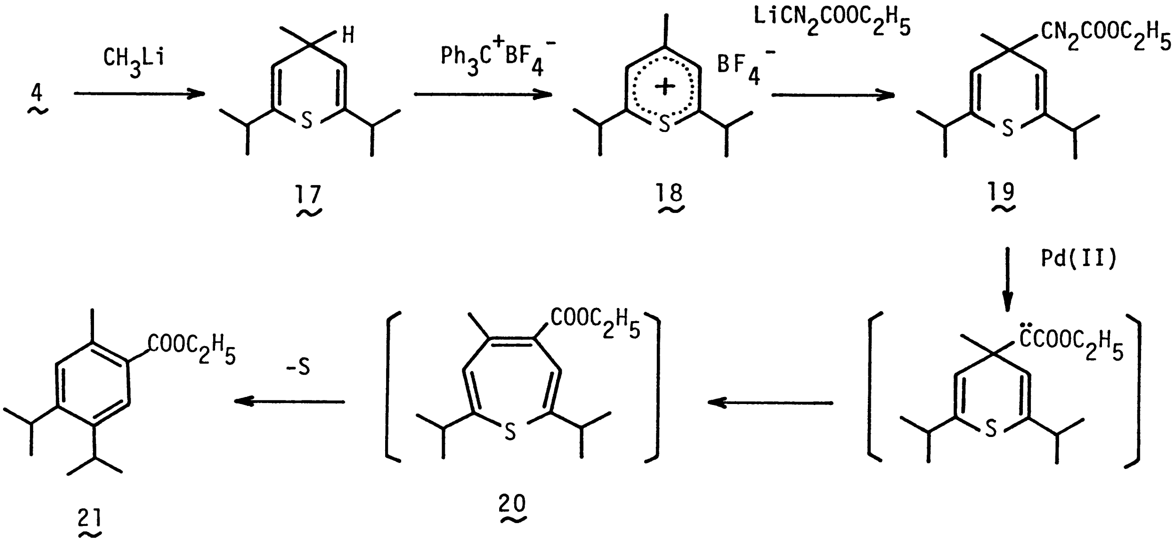
^{1}H-NMR spectrum [δ(CCl$_4$)=1.14 (12H, d, J=6.1 Hz), 1.24 (3H, t, J=7.2 Hz), 2.45 (2H, sept, J=6.1 Hz), 3.98 (1H, t, J=5.0 Hz), 4.16 (2H, q, J=7.2 Hz), and 5.44 (2H, d, J=5.0 Hz)].

Although 14 seems to be a likely precursor for the synthesis of 4-ethoxycarbonyl-2,7-diisopropylthiepin, treatment of 14 with π-allylpalladium chloride dimer (5 mol %) in a 1:1 mixture of chloroform and carbon tetrachloride at room temperature affords 2,6-diisopropyl-4-ethoxycarbonylmethylene-4H-pyran (16)$^{7)}$ which is originated from the carbene intermediate (15) via a hydrogen shift to the carbene center. The structure of 16 was assigned on the basis of its ^{1}H-NMR data,



δ(CCl$_4$)=1.10～1.50 (15H, m), 2.67 (2H, b. sept, J=6.5 Hz), 4.10 (2H, q, J=6.8 Hz), 5.12 (1H, bs), 6.30 (1H, bs), and 8.15 (1H, bs). Further proof of the structure of 16 was provided from its ready formation of the conjugate acid (16a), which showed ^{1}H-NMR signals at δ(CF$_3$COOH)=1.39 (3H, t, J=7.0 Hz), 1.65 (12H, d, J=7.0 Hz), 3.75 (2H, sept, J=7.0 Hz), 4.32 (2H, s), 4.41 (2H, q, J=7.0 Hz), and 8.52 (2H, s). In order to prevent the hydrogen shift, a methyl group was introduced at 4-position of 14.$^{12)}$ Treatment of 4 with methyllithium in ether at -40°C yielded

2,6-diisopropyl-4-methyl-4H-thiopyran (**17**),[7] labile colorless oil, δ(CCl_4)=1.10 (15H, d, J=6.1 Hz), 2.35 (2H, b. sept, J=6.1 Hz), 2.85 (1H, qt, J=6.1, 4.0 Hz), 5.27 (2H, dd, J=4.0, 0.5 Hz), which was converted into the corresponding thiopyrylium tetrafluoroborate (**18**),[7] colorless crystals, mp 99-101°C, λ_{max} (CH_3CN)= 261 nm (log ε 3.90) 302 (3.93); δ(CF_3COOH)=1.61 (12H, d, J=7.0 Hz), 2.92 (3H, s), 3.68 (2H, sept, J=7.0 Hz), 8.35 (2H, s), with trityl tetrafluoroborate in acetonitrile. The cation **18** was treated with ethyl lithiodiazoacetate as in the case of **4** to give the diazo compound (**19**), yellow oil, ν=2080, 1695 cm^{-1}; δ(CCl_4)=1.17 (12H, d, J=7.0 Hz), 1.27 (3H, t, J=7.0 Hz), 1.52 (3H, s), 2.51 (2H, sept, J=7.0 Hz), 4.18 (2H, q, J=7.0 Hz), 5.46 (2H, s), which was treated with the palladium complex.



Progress of the reaction could be monitored by ^1H-NMR spectroscopy. In a typical experiment, to a cold solution of 50 mg of **19** in a 4:2:1 mixture of CD_2Cl_2-$CDCl_3$-CCl_4 (0.42 ml) at -110°C there was added 7 mg of π-allylpalladium chloride dimer under nitrogen. At this temperature, only signals attributable to **19** were observed. Warming the reaction mixture to -70°C for 30 min leads to gradual decrease of these signals due to **19** and appearance of new signals. These new signals remained almost unchanged for at least 1.5 h at this temperature, but gradually increased at -50°C during 0.5 h. All the absorptions due to **19** were finally replaced by the new set of signals, δ=1.25 (6H, d, J=6.0 Hz), 1.27 (6H, d, J=6.0 Hz), 1.40 (3H, t, J=7.0 Hz), 3.25 (2H, sept, J=6.0 Hz), 2.55 (3H, s), 4.32 (2H, q, J=7.0 Hz), 7.07 (1H, s), and 7.78 (1H, s), apparently consistent with ethyl 2-methyl-4,5-diisopropylbenzoate (**21**), at room temperature. Work-up of the reaction mixture leads to isolation of pure **21**, colorless oil, in 70% yield. Although, in addition to the signals due to **21**, two unidentified small signals[13] appeared at δ=8.8 and 8.9 ppm during course of the reaction, no evidence for formation of the thiepin (**20**) could be observed. However, the formation of **21** is one of the strongest piece of evidence in support of the intermediary of the thiepin **20**.

These results suggested that the thiepin (**20**) can not be survived even at

-70°C and the rate of conversion of **20** to **21** is too fast to be detected **20** at this temperature. Therefore, it is concluded that the stabilizing effect of two isopropyl groups situated at 2- and 7-positions of a thiepin ring is not sufficient to permit detection of **20**. We are proceeding now to the synthesis of a thiepin having more bulky t-butyl groups at 2- and 7-positions.

References and Notes

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13) These two singlets are obviously at too low field for the thiepin **20**. We have not been able to make a definite assignment of these signals at present.

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