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Conference Paper

A Remarkably Stable and Simple Monocyclic Thiepin. Synthesis and Properties of 2,7-Di-*tert*-butyl-4-ethoxycarbonyl-5-methylthiepin[1]*

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A simple monocyclic 8π electron thiepin, 2,7-di-*tert*-butyl-4--ethoxycarbonyl-5-methylthiepin (*13*) stabilized by two bulky *tert*--butyl groups at 2- and 7-positions, was synthesized from 2,6-di--*tert*-butyl-4-methylthiopyrylium tetrafluoroborate (*11*). In spite of of its monocyclic thiepin structure, the compound *13* showed remarkable thermal stability and had a half-life of 7.1 h at 130 °C. Judging from the ^{1}H-NMR spectrum, the thiepin *13* is considered to be an atropic molecule.

Synthetic details of *11* and *13*, and the chemical and physical properties of *13* are also described.

Recently, the question of the antiaromaticity of sulfur heterocyclic 8π electron system, thiepin, has been a subject of interest for both synthetic and theoretical chemists.

The apparent instability of the thiepin ring system is in good agreement with theoretical calculations. Thus, Dewar and Trinajstić[2] reported that the thiepin is found to be weakly antiaromatic (RE = — 1.45 kcal/mol) based on the Pariser-Parr-Pople type calculations. On the other hand, Hess, Jr. and Schaad[3] have found it to be substantially antiaromatic (RE = — 0.232β) by using the Hückel MO method. The latter result is also supported by a graph theoretical treatment of Aihara.[4]

Despite the extensive studies concerning azepines[5] and oxepins,[6] little is known about thiepins[7] because of their pronounced thermal instability due to ready sulfur extrusion.[8] Although some thiepin derivatives annelated with aromatic ring have been isolated, parent thiepin has never been synthesized.[7] In order to gain insight into the detailed properties of thiepin, the synthesis of a simple monocyclic thiepin is required.

It was generally accepted that the valence isomerization of the thiepin ring into its corresponding thianorcaradiene tautomer is considered to play an essential role in a facile sulfur extrusion.[9] Examination of the molecular models of a thiepin possessing two bulky groups at 2- and 7-positions indicate

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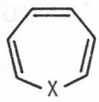
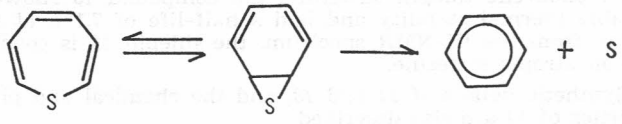
that these groups force the nonbonding interaction in the corresponding thianorcaradiene structure to be large, and hence the thiepin structure will be favored.



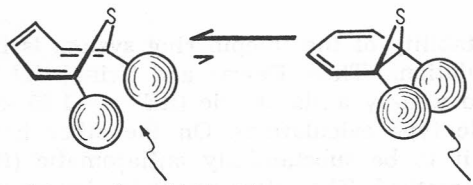
8π electron heterocycles:

X = O : oxepin
X = NH: azepine
X = S : thiepin

Dewar, Trinajstić:	Hess, Jr., Schaad:	Aihara:
(P-P-P)	(Hückel)	(Graph)
weakly antiaromatic	substantially antiaromatic	substantially antiaromatic
RE=-1.45 kcal/mol	RE = -0.232β	RE = -0.209 ~ -0.232β

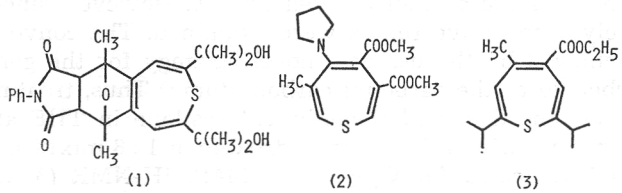


thiepin thianorcaradiene



This concept has already been revealed by the successful synthesis and isolation of a stable but heavily substituted thiepin derivative (*1*) by Schlessinger et. al.,[10] whereas the thiepin having no bulky groups at these positions such as *2* never has been isolated though it can be generated and was detected by NMR spectroscopy at — 30 °C by Reinhoudt and Kowenhoven.[11]

Furthermore, we have previously shown that the thiepin *3* having two isopropyl groups at 2- and 7-positions readily undergoes sulfur extrusion to give ultimately the corresponding benzene derivative even at — 70 °C.[12] It means that the bulkiness of an isopropyl group is not sufficient to permit isolation of the monocyclic thiepin.[13] We would like to report the first example of a simple monocyclic thiepin stabilized by two bulky *tert*-butyl groups.



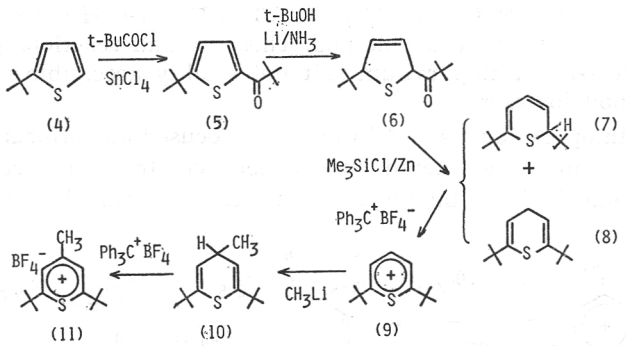
(1) (2) (3)

Schlessinger et al., JACS., 92, 5263 (1970) (isolated)

Reinhoudt et al., Chem. Comm., 1233 (1972); Tet., 30, 2093 (1974) (detected at -30°C)

Murata et al., Chem. Lett., 723 (1978) (not detected even at -78°C)

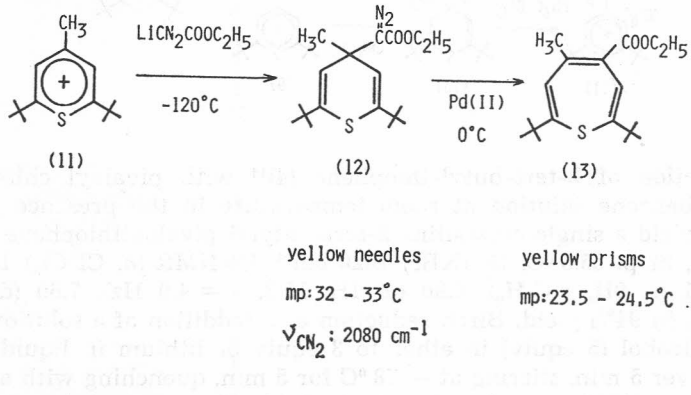
The construction of the key intermediate in our synthesis, 2,6-di-*tert*-butyl-4-methylthiopyrylium salt (*11*), is illustrated in Scheme I. The Friedel-



-Crafts reaction of 2-*tert*-butyl-thiophene (*4*)[14] with pivaloyl chloride upon stirring in benzene solution at room temperature in the presence of stannic chloride to yield a single crystalline 2-*tert*-butyl-5-pivaloylthiophene (*5*) (colorless needles, m. p. 65.5 °C, IR (KBr) 1620 cm^{-1}, ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 9H, *t*-C_4H_9), 1.41 (s, 9H, *t*-C_4H_9), 6.90 (d, 1H, H-3, J = 4.0 Hz), 7.60 (d, 1H H-4, J = 4.0 Hz)), in 94% yield. Birch reduction of *5* (addition of a solution of *5* and *tert*-butyl alcohol (5 equiv) in ether to 3 equiv of lithium in liquid ammonia at — 78 °C over 5 min, stirring at — 78 °C for 5 min, quenching with ammonium chloride) gave (88%) 2-*tert*-butyl-5-pivaloyl-2,5-dihydrothiophene (*6*) (colorless liquid, *m/e* 226.1404 (calcd for $C_{13}H_{22}OS$ 226. 1391, ^{1}H-NMR (δ, $CDCl_3$) 0.98 (s, 9H, *t*-C_4H_9), 1.20 (s, 9H, -CO-*t*-C_4H_9), 4.19 (dt, 1H H-2, J_{25} = 3.5, $J_{23} = J_{24} =$ = 1.5 Hz), 4.91 (dt, 1H, H-5, J_{52} = 3.5, $J_{54} = J_{53}$ = 1.5 Hz), 5.55 (dt, 1H, H-3, J_{34} = 4.0, $J_{32} = J_{35}$ = 1.5 Hz), 5.89 (dt, 1H, H-4, J_{43} = 4.0, $J_{45} = J_{53}$ = 1.5 Hz)) contaminated with small amounts (< 5%) of the corresponding 2,3- and 4,5--dihydrothiophenes. The compound *6* could be used in the subsequent reaction without further purification. The next step of the synthesis, ring expansion of *6* to the thiopyrans *7* and *8*, was originally attempted using the carbonium

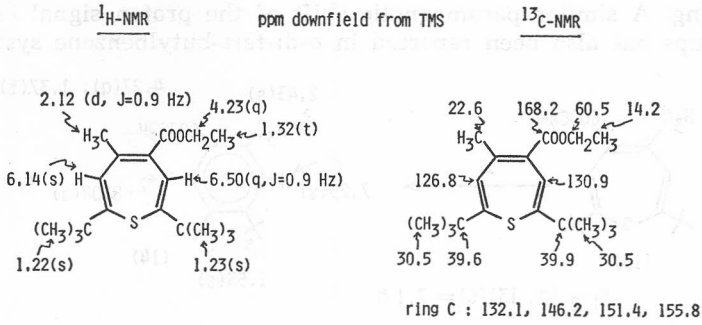
ion rearrangement of the alcohol derived from *6*. However, since this method failed completely, alternative routes were examined. The conversion of *6* into *7* and *8* was achieved by the use of a novel strategy for the generation of an organozinc carbenoid at the carbonyl carbon atom.[15] Thus, treatment of *6* with a large excess of zinc dust and trimethylchlorosilane in THF at 0 °C for 3 h gave, after quenching with 1N sodium hydroxide, a 1 : 8 mixture of *7* (colorless liquid, *m/e* 210.1443 (calcd for $C_{13}H_{22}S$ 210.1441), ^{1}H-NMR (δ, $CDCl_3$) 1.20 (s, 18H, two *t*-C_4H_9), 2.60 (t, 2H, H-4,4′, J = 8.0 Hz), 5.63 (t, 2H, H-3.5, J = 8.0 Hz)) and *8* (colorless liquid, *m/e* 210. 1440, ^{1}H-NMR (δ, $CDCl_3$) 1.12 (s, 9H, *t*-C_4H_9), 1.18 (s, 9H, *t*-C_4H_9), 3.20 (m, 1H, H-2), 5.60 (m, 3H, H-3,4,5)) in 86% yield which could be separated by column chromatography on silica gel with hexane. Hydride abstraction of the mixture of *7* and *8* with trityl tetrafluoroborate in acetonitrile afforded the thiopyrylium salt (*9*) (colorless needles, m. p. 177.5 °C, ^{1}H-NMR (δ, CF_3CO_2H) 1.69 (s, 18H, *t*-C_4H_9), 8.66 and 8.84 (A_2B, H-3,5 and 4, $J_{34} = J_{45}$ = 4.1 Hz)) in 68% yield. Methylation of *9* with methyllithium in ether at — 78 °C gave the thiopyran *10* (colorless liquid, ^{1}H-NMR (δ, CCl_4) 1.06 (s, 18H, *t*-C_4H_9), 1.20 (d, 3H, —CH_3, J = 12.0 Hz), 2.59 (tq, 1H, H-4, J = 12.0 and 3.9 Hz), 5.38 (bd, 2H, H-3,5, J = 3.9 Hz)) which was finally converted into the desired 2,6-di-*tert*-butyl-4-methylthiopyrylium tetrafluoroborate (*11*) (colorless needles, m. p. 134—135 °C, ^{1}H-NMR (δ, CF_3CO_2H) 1.73 (s, 18H, *t*-C_4H_9), 2.99 (s, 3H, -CH_3), 8.58 (s, 2H, H-3,5)) by the usual method. These overall reactions pave the way to the 2,6-di-*tert*-butylthiopyrylium salt not readily accessible via previously available methodologies.[16]

With the thiopyrylium salt *11* in hand we focused our efforts on the transformation of *11* into the thiepin ring system via the sequence of reactions shown in Scheme II. The thiopyrylium salt *11* was treated with ethyl lithio-

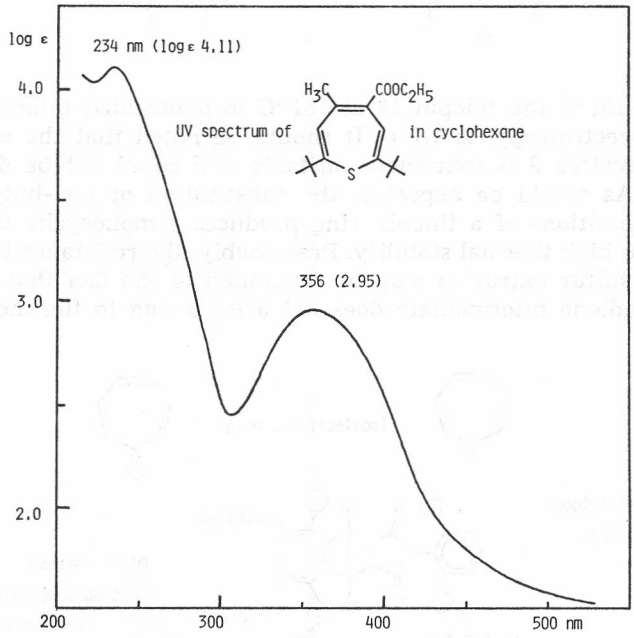


diazoacetate using conditions reported by us previously[12,17] to give diazo compound *12*, yellow needles, m. p. 32—33 °C in 90% yield. The ^{1}H-NMR (δ 1.21 (s, 18H, *t*-C_4H_9), 1.25 (t, 3H, -CH_2-CH_3, J = 7.2 Hz), 4.18 (q, 2H, -CH_2-CH_3, J = 7.2 Hz), 1.28 (s, 3H, -CH_3), and 5.53 (s, 2H, -CH=)) and IR (ν_{CN_2} 2080 cm^{-1}) data were consistent with the structure *12*. Final ring enlargement of *12* was achieved as follows. The treatment of 12 with π-allylpalladium chloride dimer (5 mol %) in chloroform at — 60 °C and stirring at 0 °C for 1 h gave thiepin *13* as yellow prisms of m. p. 23.5—24.5 °C quantitatively.

The structure of *13* was supported by the elemental analysis and ^{1}H- and ^{13}C-NMR spectral data shown in Figure 1. Thiepin *13* exhibits ultraviolet

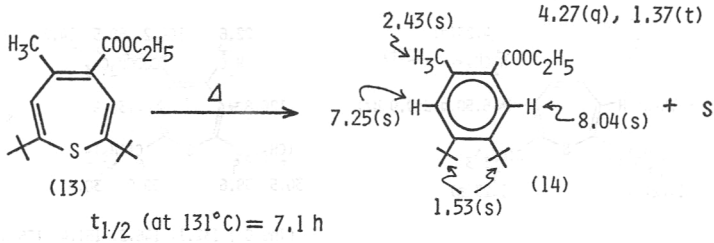


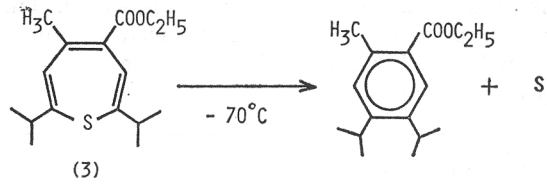
absorption maxima in cyclohexane at 234 nm (log ε 4.11) and 356 (2.95) with very low-intensity with tailing to 510 nm (Figure 2). This behavior is quite parallel to the UV spectrum of *1* which showed tailing to 500 nm.[10] The IR spectrum of *13* (in KBr) shows typical absorption for an α,β-unsaturated ester carbonyl group at 1715 cm^{-1}.



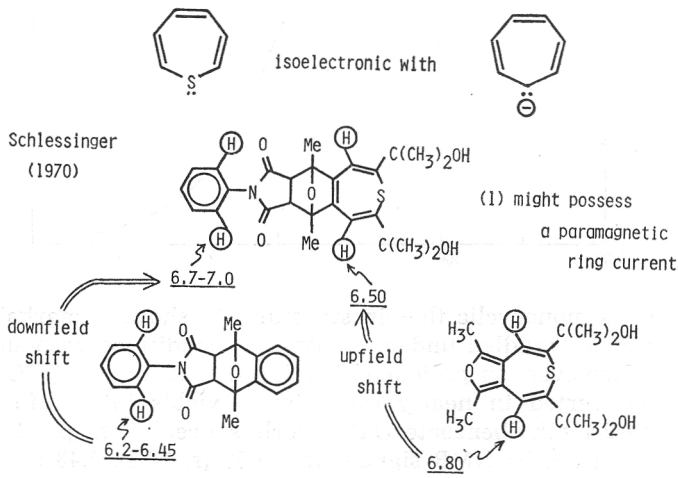
In spite of its monocyclic thiepin structure, *13* shows remarkable thermal stability and can be handled under atmospheric conditions without detectable decomposition. However, on prolonged heating in toluene at 140 °C in a sealed tube *13* was converted in nearly quantitative yields into sulfur and ethyl 4,5-di-*tert*-butyl-2-methylbenzoate (*14*), colorless needles, m. p. 21—22 °C. The compound *14* discloses ^{1}H-NMR signals at δ 1.53 (s, 18H), 2.43 (s, 3H), 7.25 (s,

1H), 8.04 (s, 1H) along with the ethyl ester protons at 1.37 and 4.27 (J = 7.0 Hz). The relatively downfield chemical shift of the *tert*-butyl groups permits the assignment of the ortho arrangement to the two *tert*-butyl groups of the benzene ring. A similar paramagnetic shift of the proton signal of the *tert*--butyl groups has also been reported in *o*-di-*tert*-butylbenzene systems.[18]

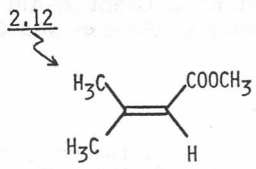


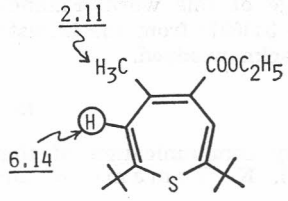


The half-life of the thiepin *13* at 131 °C in deuterated toluene, monitored by ^{1}H-NMR spectroscopy, is 7.1 h. It should be noted that the corresponding isopropyl derivative *3* is extremely unstable and could not be detected even at — 70 °C.[12] As would be expected, the substitution of *tert*-butyl groups on the 2- and 7-positions of a thiepin ring produces a monocyclic thiepin which has substantial high thermal stability. Presumably, the resistance to aromatization of *13* via sulfur extrusion may be attributed to the fact that formation of the thianocaradiene intermediate does not arise owing to the increased steric hindrance.

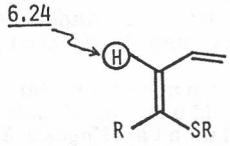


Finally, I should like to add some comments on the antiaromaticity of thiepin. The thiepin is isoelectronic with the 8π electron cycloheptatrienide ion of *13* via sulfur extrusion may be attributed to the fact that formation of concluded that the thiepin ring proton of *1* resonates at a higher field (δ 6.50) than that of its precursor furanothiepin (δ 6.80). In addition, the ortho protons of the imide phenyl group in *1* resonate at a lower field (δ 6.70—7.00) than comparable protons of the corresponding benzenoid derivative (δ 6.20—6.45); these were taken as indicative of the presence of a paramagnetic ring current.





substituent shielding coefficient Z :



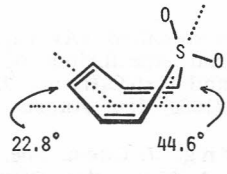
Z_{gem} (-C=C-) = +1.26

Z_{cis} (alkyl) = -0.26

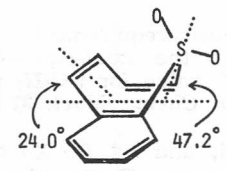
Z_{trans} (-SR) = -0.04

$\delta = 5.28 + 0.96 = 6.24$ $\quad \Sigma Z = +0.96$

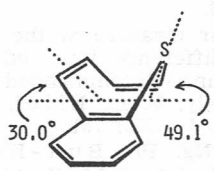
However, the methyl protons of *13* resonate at δ 2.11 which is very similar to the value reported for the methyl group cis to methoxycarbonyl in methyl 3,3-dimethylacrylate (δ 2.12).[19] Furthermore, the chemical shift of the ring



Mock et al.,
JACS., 90, 4501 (1965)

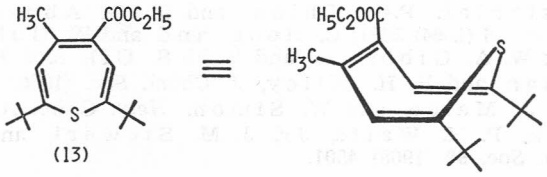


Kasai et al.,
Acta Cryst.,
B31, 2729 (1975)



Kasai et al.,
Angew. Chem.,
88, 295 (1976)

the thiepin (13) must exist in a boat conformation



proton (H-6) of *13* (δ 6.14) is in fair agreement with the value (δ 6.24) calculated by using the substituent shielding coefficient Z[20] for olefinic protons.

In addition, available X-ray crystallographic results of thiepin 1,1-dioxide,[21] benzo[*b*]thiepin 1,1-dioxide,[22] and parent benzo[*b*]thiepin[23] suggested that *13* must exist in a boat conformation. From these results we consider the thiepin *13* to be an atropic (an olefinic) molecule.

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SAŽETAK

Neobično stabilan i jednostavan monociklički tiepin. Priprava i svojstva 2,7-di-*t*-dutil-4-etoksikarbonil-5-metiltiepina

I. Murata, K. Nishino, S. Yano, Y. Kohashi i K. Yamamoto

Jednostavni monociklički tiepin s 8 π elektrona, 2,7-di-*t*-butil-4-etoksikarbonil-5-metiltiepin (I), pripravljen iz 2,6-di-*t*-butil-4-metiltiopirilijum tetrafluoroborata (II). Uprkos tiepinskoj strukturi spoj I pokazao je neobičnu termičku stabilnost. Prikazani su detalji priprave spojeva I i II, kao kemijska i fizikalna svojstva spoja I.

ODJEL ZA KEMIJU
SVEUČILIŠTE U OSAKI
OSAKA, JAPAN

Prispjelo 3. rujna 1979.