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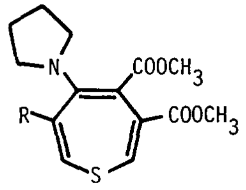
THIEPIN X1). SYNTHESES AND THERMAL STABILITY OF ETHOXYCARBONYLBENZO[*b*]THIEPINS

Keitaro Nishino, Kazuhiro Nakasuji, and Ichiro Murata*

Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

Recently, Reinhoudt and Kouwenhoven2) have reported the successful synthesis of 3,4-bis-(methoxycarbonyl)-5-pyrrolidin-1-ylthiepins (*1*) as the first example of monocyclic thiepin. These authors have noted that "*the relatively high stability of these thiepins (1) is attributed to the presence of the two methoxycarbonyl groups which cause a decrease in electron density of the 8π-electron system, as a result of which the formal anti-aromatic character is reduced*". Traynelis and co-workers3) have also reported a slight increase in thermal stability of benzo[*b*]thiepin when electron withdrawing groups are present. It has subsequently been shown that resonance energy calculations on some thiepin derivatives predict that thiepins substituted with electron withdrawing groups will be less anti-aromatic than the parent thiepin.4) Despite these studies, we have shown that at least benzo[*b*]thiepin can be stabilized by electron donating methyl group whereas electron withdrawing formyl substitution leads to a decrease in stability of benzo[*b*]thiepin.5) To gain systematic understanding of the substituent effect on stability of thiepin system, we have investigated the syntheses6) of a series of ethoxycarbonylbenzo[*b*]thiepins.

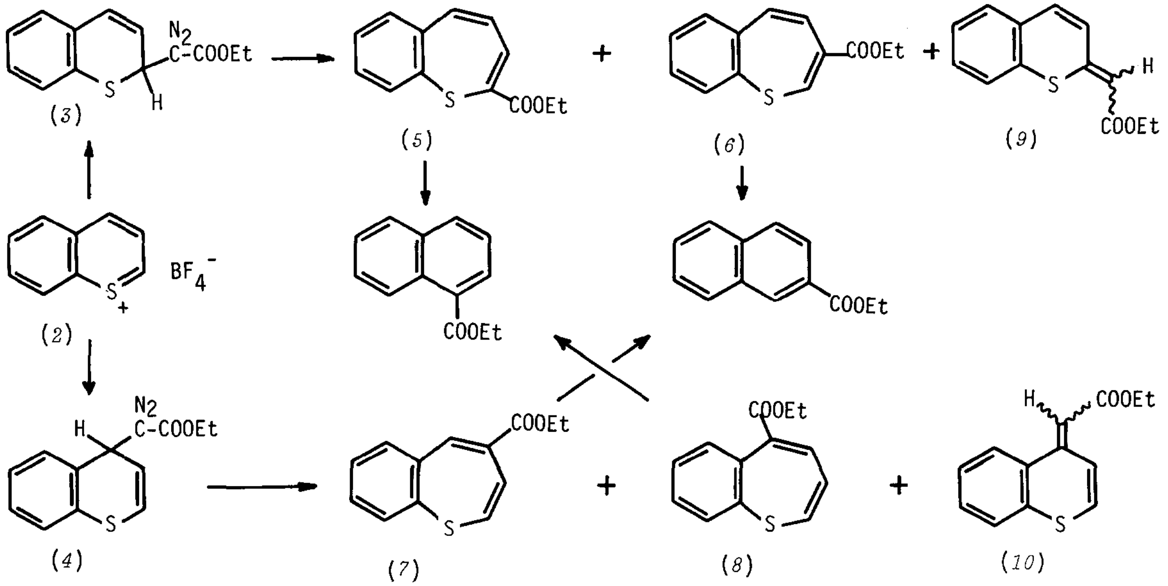


R=CH_3
R=H

(*1*)

Benzo[*b*]thiopyrylium tetrafluoroborate (*2*), which is obtained in essentially quantitative yield by treatment of benzo[*b*]thiopyran with trityl tetrafluoroborate in anhydrous acetonitrile, was treated in a 2:1 mixture of THF and ether at -120∿-110°C with ethyl lithiodiazoacetate followed by stirring at -100°C for 9 h. Chromatography of the product on silica gel (deactivated with 6% water) using a 3:1 mixture of hexane-benzene as eluent allowed the separation of two isomeric diazo compounds, (*3*) [yellow needles, mp 29-30°C, $\nu(CCl_4)$=2090, 1690 cm^{-1}; λ_{max}(cyclohexane)=212,243, 330 (sh), 408 nm; $\delta(CCl_4)$=1.27 (3H, t, J=7.1 Hz), 4.23 (2H, q, J=7.1 Hz), 4.61 (1H, d, J=6.5 Hz), 5.97 (1H, dd, J=6.5, 10.0 Hz), 6.72 (1H, d, J=10.0 Hz), 7.03-7.19 (4H, m)] and (*4*) [yellow needles, mp 40-40.5°C; $\nu(CCl_4)$=2090, 1690 cm^{-1}; λ_{max}(cyclohexane)=222, 260, 410 nm; $\delta(CCl_4)$=1.25 (3H, t, J=7.1 Hz), 4.18 (2H, q, J=7.1 Hz), 4.63 (1H, d, J=6.0 Hz), 6.02 (1H, dd, J=6.0 10.0 Hz), 6.59 (1H, d, J=10.0 Hz), 7.10-7.43 (4H, m)], each in 35% yield.

Treatment of *3* with π-allylpalladium chloride dimer (2 mole %) in chloroform at -60°C and allowing to stir at -60~-30°C for 6 h afforded 2- (*5*) and 3-ethoxycarbonylbenzo[*b*]thiepin (*6*) in 27% and 19% yield, respectively, after low temperature column chromatography (-30°C) on alumina with a 7:1 mixture of light pet. ether-methylene chloride.[7] In an exactly same procedure, the alternate diazo compound (*4*) also underwent rearrangement in the presence of palladium catalyst to a mixture of products which was separated into 4- (*7*) and 5-ethoxycarbonylbenzo[*b*]thiepin (*8*) in 31% and 15% yield, respectively.[7] Owing to the competitive hydrogen shift to the intermediate carbene,[8] separation of the mixture of above reaction products from *3* and *4* led to isolation of the exo-methylene compound, (*9*) [yellow needles, mp 53-4°C; ν(KBr)=1675 cm^{-1}; $\delta(CCl_4)$=1.30 (3H, t, J=7.0 Hz), 4.12 (2H, q, J=7.0 Hz), 5.68 (1H, s), 6.49 (1H, d, J=10.0 Hz), 6.79 (1H, d, J=10.0 Hz), 7.12-7.60 (4H, m)] and (*10*) [colorless prisms, mp 141-2°C; ν(KBr)=1710 cm^{-1}; $\delta(CCl_4)$=1.06 (3H, t, J=7.1 Hz), 3.96 (2H, q, J=7.1 Hz), 4.96 (1H, s), 6.08 (1H, d, J=10.3 Hz), 6.15 (1H, d, J=10.3 Hz), 7.21-7.38 (4H, m)], respectively.



Although all of these thiepins isolated are yellow crystalline compounds, melting point determinations and elemental analyses could not be made except 2-substituted thiepin (*5*) due to their pronounced thermal instability. However, structures of all four thiepins are unambiguously established by consistent ^{1}H-NMR data obtained at -30°C (see Table-1), in addition to their ready conversions to either ethyl α-naphthoate or ethyl β-naphthoate at room temperature.

Table-1. Physical Properties of Ethoxycarbonylbenzo[*b*]thiepins

	appearance	mp (°C)	^{1}H-NMR Parameters$^{a)}$						
			H-2	H-3	H-4	H-5	Arom-H	coupl.const.	CH_2 CH_3
2-COOEt *(5)*	yellow prisms	54- 54.5		7.41 (d)	6.50 (dd)	7.24 (d)	7.18-7.50 (m)	$J_{3,4}$=5.8 $J_{4,5}$=11.9	4.26 1.32 J=7.2
3-COOEt *(6)*	yellow prisms		7.28 (s)		6.84 (d)	7.21 (d)	7.09-7.39 (m)	$J_{4,5}$=12.4	4.28 1.31 J=7.2
4-COOEt *(7)*	yellow needles		6.05 (d)	6.91 (d)		8.24 (s)	7.14-7.28 (m)	$J_{2,3}$=9.0	4.32 1.37 J=7.2
5-COOEt *(8)*	yellow needles		6.39 (d)	6.55 (dd)	7.66 (d)		7.37 (bs)	$J_{2,3}$=9.0 $J_{2,4}$=0.3 $J_{3,4}$=5.4	4.34 1.36 J=7.1

a) Chemical shifts reported in ppm from internal TMS in $CDCl_3$.
Coupling constants reported in hertz.

Syntheses of a series of ethoxycarbonylbenzo[*b*]thiepins made it possible to compare their thermal stabilities in terms of half-lives of sulfur extrusion reaction which could be monitored by ^{1}H-NMR spectroscopy at appropriate temperatures. The results thus obtained are summarized in Table-2, along with the previously reported data$^{5)}$ for the parent benzo[*b*]thiepin and its methyl and formyl derivatives.

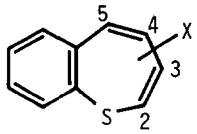


Table-2. Half-lives of Benzo[*b*]thiepin Derivatives (min)

X	Temp. (°C)	3-X	4-X	5-X	parent	2-X
$COOC_2H_5$	27	16				
	37	a)	58	69	182	b)
	47				58	352
CH_3	47	100	62	67	58	
CHO	47		49		58	

a) too fast to be measured. b) too slow to be measured.

It is clear from Table-2 that the benzo[*b*]thiepin system is stabilized by electron-donating methyl group whereas the reverse is true for π-accepting ethoxycarbonyl group except 2-substituted thiepin (*5*). Furthermore, stabilizing and destabilizing effects caused by methyl and ethoxycarbonyl groups, respectively, were most prominent when these groups are substituted at 3-position. In both series of benzo[*b*]thiepins comparable stabilities are found between 4- and 5-substituted derivatives. A substantial increase in thermal stability of 2-ethoxycarbonyl derivative (*5*) compared with the parent benzo[*b*]thiepin may be attributed to steric9) and electronic effect10) of the ethoxycarbonyl group situated on a carbon adjacent to the sulfur of the thiepin ring.11)

References and Notes

1) Part IX: S. Yano, K. Nishino, K. Nakasuji, and I. Murata, *Chemistry Lett.*, in press (1978).

2) D. N. Reinhoudt and C. G. Kouwenhoven, *J. Chem. Soc., Chem. Commun.*,1232, 1233 (1972); idem., *Tetrahedron.*, 30, 2093 (1974).

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4) B. A. Hess, Jr., L. J. Schaad, and D. N. Reinhoudt, *Tetrahedron*, 33, 2683 (1977).

5) I. Murata and T. Tatsuoka, *Tetrahedron Lett.*, 2697 (1975).

6) Our synthetic method of the thiepin system is based on the utilization of palladium catalyzed ring expansion of diazo compounds, Cf. K. Nakasuji, K. Kawamura, T. Ishihara, and I. Murata, *Angew. Chem.*, 88, 650 (1976); *Angew. Chem., internat. Edit.*, 15, 611 (1976).

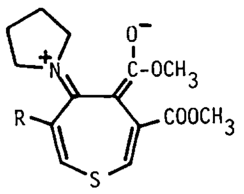
7) All manipulations during work-up have to be carried out below -30°C in order to avoid decomposition of the thiepins.

8) See, reference (1).

9) It is generally accepted that the stability of the thiepin ring can be enhanced by introduction of two bulky groups at 2- and 7-positions of the thiepin, Cf. J. M. Hoffmann and R. H. Schlessinger, *J. Am. Chem. Soc.*, 92, 5263 (1970).

10) R. Hoffmann and co-workers suggested that substitution on thiirane ring by π-acceptor groups would lead to a weaker C-C bond, and hence the thiepin form will be favored in equilibrium with thianorcaradiene form which is thought to be a possible intermediate for thermal sulfur extrusion reaction of the thiepin system. R. Hoffmann, H. Fujimoto, J. R. Swenson, and C-C. Wan, *J. Am. Chem. Soc.*, 95, 7644 (1973).

11) We feel that the relatively high stability of (1) can be ascribed in part to the presence of a resonance contributor such as (i) arising from the "push-pull" effect of the adjacent pyrrolidinyl and methoxycarbonyl groups.



(i)

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