A SIMPLE ONE-POT SYNTHESIS OF HYDROISOBENZOTHIOPHENES <u>VIA</u> THREE-STEP SEQUENTIAL PERICYCLIC REACTIONS OF XANTHATES

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Summary: Thermolysis of \underline{O} -(2,4-alkadienyl) \underline{S} -(2-alkenyl or 2-alkynyl) dithiocarbonates (xanthates) gave the hydroisobenzothiophene derivatives <u>via</u> two sequential [3,3]-sigmatropic rearrangement followed by the intramolecular cycloaddition.

Pericyclic reactions have been widely employed in synthesis because of their pronounced regio- and stereoselectivity. In particular, intramolecular Diels-Alder reactions (IMDA) are extensively studied from theoretical and synthetic view points and provide powerful synthetic methodology for the construction of complex polycyclic molecules.¹⁾

Recently, we have reported a new and simple synthetic method of allylic sulfides.^{2a)} The reaction involves two-step sequential [3,3]-sigmatropic rearrangement reactions of allylic xanthates.^{2c)} The reaction proceeds with high regioselectivity giving rise only to the allylic isomer. Combination of this reaction and the IMDA reaction would provide a powerful tool for regio- and stereocontrolled routes to fused or bridged heterocyclic systems containing sulfur atom (Scheme 1).



This paper describes a new and convenient synthetic route of hydroisobenzothiophenes using three-step sequential pericyclic reactions of $\underline{0}$ -(2,4-alkadienyl) \underline{S} -(2alkenyl or 2-alkynyl) dithiocarbonates. The xanthates of 2,4-alkadienols were easily prepared according to the previously reported method.^{2c)} The xanthates synthesized underwent [3,3]-sigmatropic rearrangement to give the corresponding dithiol esters even at room temperature. Heating the dithiol esters at $110-200^{\circ}C$ with/without catalysts resulted in extrusion of COS gas giving bicyclic compounds, <u>i.e.</u>, hydroisobenzothiophene derivatives <u>via</u> formation reaction of 2,4-alkadienyl 2-(alkenyl or alkynyl) sulfides (see Table I).

Exp.	P	Xanthate (I)	Temp.	Catalyst ^{a)}	Time	Product ^{b)}	cis:trans
HO.	11	IL [*]	(0)	(mor)	(n)	(lield %)	ratio
1	н	CH≣CCH ₂ - (Ia)	190	PNP(0.4)	0.25	IVa (47)	
2		сн ₂ =снсн ₂ - (Ib)	RT	MeAlCl ₂ (1.0)	1	IIIb(46) ^{c)}	
2'	Su	lfide (IIIb)	Toluene ^{d)}	~	35	IVb (55) ^{e)}	40:60
3	Me	CH≣CCH ₂ - (Ic)	180	PNP(0.5)	0.25	IVc (62)	-
4		CH ₂ =CHCH ₂ - (Id)	CHCl3 ^{d)}	AlCl ₃ (1.0)	4.5	IIId(17) ^{c)}	
5		CH2=CHCH2-	190	PNP(1.0)	0.25	IVd (12) ^{e)}	38:62
6		CH2=CHCH2-	200		_ f)	IVd (59) ^{e)}	28:72
7		PhCH=CHCH ₂ - (Ie)	Toluene ^{d)}		52	IVe (36)	
8		EtO(O=C)CH=CHCH ₂ - (If)	200		_ f)	IVf (60) ^{e)}	43:57
9		EtO(0=C)CH=CHCH ₂ - (If)	100	PNP(1.0)	4	IVf (64) ^{e)}	36:64
10		$EtO(0=C)CH=CHCH_2^{-}$ (If)	CHC13 ^{d)}	AlCl ₃ (1.0)	2	IVf (41) ^{e)}	5:95

Table I. Thermolysis of the Xanthates [RCH=CHCH=CHCH20(C=S)SR'] (I)

a) PNP: <u>p-Nitrophenol.^{2b)}</u> b) Isolated yields. c) Yield of the sulfide. d) Reflux. e) A mixture of <u>cis</u>-fused and <u>trans</u>-fused IMDA adducts. f) Distillation at reduced pressure.



The products were purified by chromatography on silica gel and isolated as colorless oils.

The formation of hydroisobenzothiophenes were confirmed by the ¹H or ¹³C-NMR spectral data.³⁾ Heating <u>S</u>-propargyl xanthate (Ia) of (2E,4E)-pentadienol at 190°C in the presence of p-nitrophenol^{2b)} (PNP) afforded IVa (Exp. 1). In the case of <u>S</u>-allyl xanthate (Ib), a similar treatment yielded a trace of IVb. In contrast, the use of MeAlCl₂ catalyst caused extrusion of COS at room temperature giving (2E,4E)-pentadienyl allyl sulfide (IIIb) (Exp. 2), which cyclized at 110°C to give <u>cis</u>- and <u>trans</u>-fused adducts (40:60) (IVb) (Exp. 2'). The molecular mechanics (MM2) calculations⁴⁾ on four possible IMDA cycloadducts (<u>cis/trans</u> and fused/bridged bicyclic ring systems) derived from IIIb indicate that the <u>trans</u> fused cycloadduct is the most stable in terms of heat of formation.



MM2 Heats of Formation for Possible IMDA Adducts

In the reaction of <u>S</u>-propargyl xanthate of (2E, 4E)-hexadienol, the ¹H-NMR spectrum of IVc showed a methyl signal as a sharp doublet indicating the absence of the sterecisomer (Exp. 3).

Pyrolysis of the dithiol ester (IId) may produce four allylically and/or geometrically isomeric diene sulfides as the intermediate (in Exp. 5,6). When the reaction was carried out in the presence of AlCl₃ at 70°C, only (2E,4E)-hexadienyl allyl sulfide (IIId) was produced regioselectively (Exp. 4).⁵⁾ As drawn above, the diene (2E,4E)-IIId can give four IMDA adducts depending on the orientation of the dienophile relative to the diene in the transition state. The ¹H-NMR spectrum of the pyrolyzed product of IId (Id) showed two sharp signals at methyl region (<u>ca</u>. 1.00 ppm), which can be ascribable to <u>cis</u> and <u>trans</u>fused isomers (IVd). The MM2 calculation indicates the predominant formation of the <u>trans</u> isomer.

Similarly, the diene sulfide IIIe gave a mixture of the IMDA adducts, judged from the presence of two methyl signals. A definite <u>endo-exo</u> assignment has not yet been possible (Exp. 7).

Adding an electron-withdrawing group to the dienophile moiety accelerated the reac-

tions (II \rightarrow III \rightarrow IV) (Exp. 8-10). In the reactions, PNP behaved as a catalyst by hydrogen bonding to the carbonyl functions of II and IIIf (Exp. 9) and the Lewis aci catalyzed reaction proceeded under very mild reaction conditions showing the high stereoselectivity (Exp. 10). The frontier orbital theoretical view⁶) on the enhancement of the reaction rate and stereoselectivity is that coordination of AlCl₃ to the carbonyl function causes lowering of the LUMO energy level of the dienophile and polarization of the LUMO coefficients. This favors the <u>endo</u> transition state increasing the stereoselectivity of the cycloaddition (Scheme 2).



Scheme 2

Further studies are now in progress on clarification of the stereochemistry of the IMDA adducts and controlling factors intervened in the reactions.

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References and Notes

1) E. Ciganek, "Organic Reactions: The Intramolecular Diels-Alder Reaction," Vol. 32, ed. by W. C. Dauben, John Wiley and Sonc, Inc., New York, 1984, Chapter I. 2) a) K. Harano, N. Ohizumi and T. Hisano, <u>Tetrahedron Lett.</u>, 26, 4203(1985): K. Harano, N. Ohizumi, K. Misaka, S. Yamashiro and T. Hisano, <u>Chem. Pharm. Bull.</u>, 38, 619 (1990). b) K. Harano, S. Yamashiro, K. Misaka and T. Hisano, <u>ibid.</u>, 38, 2956(1990). c) K. Harano and T. Taguchi, <u>ibid.</u>, 20, 2348, 2357 (1972): <u>Idem, Ibid.</u>, 23, 467(1975). 3) The products were analyzed by 400 MHz ¹H-MMR spectrometry (in CDCl₃) and high resolution mass spectrometry (HRMS). The spectral data of typical cycloadducts are as follows. Compound IVb (trans:cis=3:2): ¹²C-MMR: 23.6, 24.1 (C₆, ratio=3:2), 26.6, 27.4 (C₅, ratio=3:2), 45.2, 35.7 (C₂, ratio=3:2), 36.0, 36.4 (C₇, ratio=3:2), 43.6, 41.0 (C_{6a}, ratio=3:2), 46.0 (C₂, ratio=3:2), 127.6 (C₄), 128.2 (C₃). HRMS m/z:M^{*} Calcd for C₈H₁₂S, 140.0671. Found 140.0660. Compound IVf: ¹H-NMR: 0.93 (3H, d, J=1.3Hz, C_5-Me), 1.28 (3H, t, J=7Hz, Me-CH₂OCO), 2.00 (1H, oct. , J=5.8, 11, 11, 11Hz, C₆), 2.23-2.29 (1H, m, C_{2a}-H), 2.47 (1H, br d, J=11Hz, C₇-H), 2.53 (1H, br d, J=5.8, 9.5 Hz C₂-H), 2.73 (1H, dd, J=5.8, 9.5Hz, C₇-H), 2.77-2.83 (1H, m, C₅-H), 2.96 (1H, dd, J=9.5Hz, C_2-H), 3.29 (1H, dd, J=5.8, 9.5Hz, C₇-H), 4.11-4.23 (2H, m, J=7.0Hz, -CH₂OCO), 5.63 (1H, ddd, J=10.2, 6, 3Hz, C₇-H), 5.72 (1H, br d, J=10.2Hz, C₂-H), 12-CMR: 14.30 (Me), 17.18 (Me), 33.52 (C₂), 133.09 (C₇), 34.21 (C₂), 42.11(C_{6a}), 47.22 (C_{2a}), 49.15 (C₆), 60.26 (CH₂Me), 126.23 (C₃), 133.09 (C₇), 34.21 (C₂), 42.11(C_{6a}), 47.22 (C_{2a}), 49.15 (C₆), 60.26 (CH₂Me), 126.23 (C₃), 133.09 (C₇), 34.21 (C₂), 42.11(C_{6a}), 47.22 (C_{2a}), 49.15 (C₆), 60.26 (CH₂Me), 126.23 (C₃), 133.09 (C₇), 34.21 (C₂), 42.11(C_{6a}), 47.22 (C_{2a}), 49.15 (C₆), 60.26 (CH₂Me), 126.23 (C₃), 133.09 (C₇), 34.21 (C₂), 42.11(C_{6a}), 47.22 (C_{2a}), 49.15 (C₆), 60.26 (CH₂Me), 126.23 (C₃), 133

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