EtOAc/hexanes) gave 722 mg (72%) of pure **23** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, 1 H, J = 3.75 Hz and J = 2.85 Hz), 4.68 (m, 1 H), 4.31 (m, 1 H), 2.72 (dm, 1 H, J = 16.8 Hz), 2.06 (d, 1 H, J = 16.8 Hz), 1.70–1.30 (m, 4 H), 1.47 (s, 9 H), 1.21 (d, 3 H, J = 7.2 Hz), 0.94 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 127.5, 123.1, 79.8, 52.7, 44.5, 38.4, 37.9, 28.4, 20.9, 20.0, 13.9; FT-IR (neat) 2966, 2934, 2874, 1695, 1479, 1457, 1407, 1367, 1343, 1318, 1177, 1116, 1100, 1070 cm^{-1}. Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.84; N, 5.12. Found: C, 61.50; H, 9.07; N, 5.17.

1-(*tert*-Butoxycarbonyl)-*cis*-2-methyl-6-*n*-propylpiperidine (26) from 1,2,5,6-Tetrahydropyridine 23. By use of a procedure similar with that described for the preparation of **15**, a mixture of 587 mg of tetrahydropyridine **23** (2.14 mmol), 590 mg of lithium carbonate, and 590 mg of 10% Pd/C in 30 mL of ethyl acetate was hydrogenated for 2 days. Purification of the crude product by MPLC (silica gel, 10% EtOAc/hexanes) gave 428 mg (83%) of **26** as a colorless oil.

Preparation of 26 from 1,2-Dihydropyridine 22. By use of a procedure similar with that described for the preparation of **15**, a mixture of 304 mg of dihydropyridine **22** (1.12 mmol), 300 mg of lithium carbonate, and 300 mg of 5% Pd/C in 20 mL of ethyl acetate was hydrogenated for 2 days. (Note: Shorter reaction times gave the incomplete reduction product 1,2,3,4-tetrahydropyridine as a significant contaminant.) The crude product consisted of a mixture of 98% cis isomer **26** and 2% of the trans isomer as determined by capillary GC analysis. Purification by MPLC (silica gel, 10% EtOAc/hexanes) gave 187 mg (69%) of **26** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.22 (m, 1 H), 4.10–4.00 (m, 1 H), 1.70–1.20 (m, 10 H), 1.46 (s, 9 H), 1.16 (d, 3 H, J = 7.2 Hz), 0.92 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 78.7, 50.0, 45.5, 37.2, 30.2, 28.4, 27.3, 20.6, 20.3, 14.1, 14.0; FT-IR (neat) 2960, 2936, 2872, 1690, 1458, 1404, 1391, 1365, 1348, 1180, 1103, 1083 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.64; H, 11.27; N, 5.80.

(±)-Dihydropinidine. *cis*-2-Methyl-6-*n*-propylpiperidine (2). To a stirred solution of 226 mg (0.936 mmol) of Boc-piperidine **26** in 15 mL of acetonitrile was added sodium iodide (562 mg, 3.744 mmol) followed by chlorotrimethylsilane (0.48 mL, 3.744 mmol). After stirring for 12 h at room temperature, saturated aqueous K_2CO_3 (5 mL) was added and stirring was continued for 1 h. The layers were separated, the aqueous phase was extracted with ether (3 × 5 mL), and the combined organic extracts were dried over K_2CO_3. Filtration through Celite and concentration on a rotary evaporator with the water bath at 0 °C gave the crude product. Kugelrohr distillation (60–100 °C, 20 mmHg (water aspirator), receiver bulb at −78 °C) gave 93 mg (70%) of **2** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.56 (m, 1 H), 2.55–2.45 (m, 1 H), 1.76 (m, 1 H), 1.60 (m, 2 H), 1.55–0.80 (m, 8 H), 1.06 (d, 3 H, J = 6.6 Hz), 0.91 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8, 52.5, 39.7, 34.4, 32.2, 24.9, 23.1, 19.1, 14.3; ^{1}H NMR (300 MHz, C_6D_6) δ 2.52–2.42 (m, 1 H), 2.40–2.32 (m, 1 H), 1.69 (m, 1 H), 1.48 (m, 2 H), 1.35–0.80 (m, 8 H), 0.99 (d, 3 H, J = 6.3 Hz), 0.88 (t, 3 H, J = 6.3 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 57.1, 52.7, 40.1, 34.8, 32.5, 25.4, 23.2, 19.3, 14.6; FT-IR (neat) 3276 (weak), 2957, 2928, 2857, 2798, 2713, 1463, 1441, 1377, 1321, 1129 cm^{-1}; (±)-dihydropinidine·HCl mp 212–213 °C (2:1 EtOAc–EtOH) (lit.[19a] mp 210–213 °C).

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Registry No. (±)-**1**, 28720-60-7; (±)-**1**·HCl, 63950-17-4; (±)-**2**, 65337-42-0; (±)-**2**·HCl, 121963-72-2; **3**, 626-61-9; (±)-**4**, 132410-08-3; (±)-**5**, 132410-09-4; (±)-**6**, 132438-34-7; (±)-**7**, 132410-10-7; (±)-**8**, 132410-11-8; (±)-**9**, 132410-12-9; (±)-**10**, 132410-13-0; (±)-**15**, 132410-14-1; (±)-**16**, 132410-15-2; (±)-**17**, 63950-16-3; (±)-**18**, 132410-16-3; (±)-**20**, 132410-17-4; (±)-**21**, 132410-18-5; (±)-**22**, 132410-19-6; (±)-**23**, 132410-20-9; (±)-**24**, 132410-21-0; (±)-**25**, 132410-22-1; (±)-**26**, 132410-23-2; $Br(CH_2)_{10}CH_3$, 693-67-4.

Thermal and Lewis Acid Induced Cycloaddition of Thioaldehyde *S*-Oxides (Monosubstituted Sulfines) to Dienes. 3[1,2]

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The stereochemical course of the 1,4-cycloaddition of thioaldehyde *S*-oxides (monosubstituted sulfines) to 2,3-dimethylbuta-1,3-diene, buta-1,3-diene, and *cis*- and *trans*-penta-1,3-diene was investigated. Unexpectedly, the reactions of buta-1,3-diene and 2,3-dimethylbuta-1,3-diene with *Z*-monoaryl sulfines afforded cis/trans mixtures of the corresponding dihydrothiopyran *S*-oxides, in which the relative amounts of the two isomers depended upon the initial diene/sulfine ratio. A *Z* to *E* isomerization of the dienophiles during the cycloaddition was responsible. On the other hand, *Z*/*E* mixtures of aliphatic *tert*-butyl sulfine gave, with 2,3-dimethylbuta-1,3-diene, only the corresponding trans cycloadduct. Catalysis of the reaction by Lewis acids, heretofore largely unexplored, was also investigated.

Introduction

Considerable attention has been payed to the chemistry of disubstituted sulfines, the literature of which has been recently reviewed.[3] In particular, the stereochemical course of the cycloaddition of unsymmetrically disubstituted sulfines to dienes has been investigated in detail,

† Deceased on March 11, 1989.

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Table I. Dependence of the Cis/Trans Distribution of the Product Dihydrothiopyran S-Oxides 2a–e on the Initial DMB/Sulfine Ratio

entry	sulfine[a] (mmol)	DMB (mmol)	DMB 1	product (2)	cis/trans ratio	yield[b] (%)	reaction time (h)
1	**1a** (0.20)	1.5	7.2	**2a**	33/66	60	
2	**1a** (0.35)	4.8	13.7	**2a**	63/37	83	
3	**1a** (0.23)	26.6	111.7	**2a**	95/5	90	70
4	**1a** (0.47)	91.1	195.0	**2a**	95/5	92	
5	**1b** (0.33)	2.0	6.1	**2b**	8/92	71	
6	**1b** (0.36)	5.3	14.5	**2b**	25/75	75	
7	**1b** (0.36)	34.0	94.0	**2b**	65/35	90	100
8	**1b** (0.36)	50.9	144.2	**2b**	81/19	90	
9	**1b** (0.25)	49.0	190.2	**2b**	82/18	90	
10	**1b** (0.31)	92.0	297.0	**2b**	95/5	96	
11	**1c** (0.39)	3.1	8.0	**2c**	23/77	70	
12	**1c** (0.41)	47.7	116.3	**2c**	42/58	82	50
13	**1c** (0.23)	57.4	251.0	**2c**	84/16	82	
14	**1d** (0.06)	3.1	54.0	**2d**	10/90	78	
15	**1d** (0.06)	132.0	230.0	**2d**	20/80	95	1000
16	**1e** (0.86)	12.2	14.4	**2e**	trans	25	
17	**1e** (1.00)	176.0	176.0	**2e**	trans	42	24

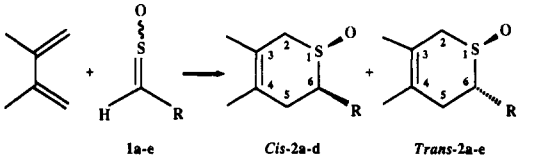
[a] Compounds **1a–c** were 99:1 *Z*/*E* mixtures, reaction temperature = 25 °C. **1d** was the pure *Z* isomer, reaction temperature = 70 °C. **1e** was a 75:25 *Z*/*E* mixture, reaction temperature = 25 °C. [b] Isolated yields.

with 2,3-dimethylbuta-1,3-diene (DMB) frequently serving as the diene reactant. High stereospecificity was commonly observed in these reactions, for the stereochemistry of the parent sulfines was retained in the cycloadducts.[3a,f]

In contrast, less information is available on the stereochemical outcome of Diels–Alder reactions of the thermally more labile monosubstituted sulfines. To our knowledge, only the reaction of propanethial *S*-oxide with very reactive cyclopentadiene has been studied.[4] The ($4\pi + 2\pi$) cycloaddition of 3,3-dimethylpropanethial *S*-oxide to electron-rich 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene[5] was also been reported, but the stereochemical outcome of the reaction was not investigated.

Recently, we developed a new method for the desilylation[1,2] of (trimethylsilyl)thioacylsilane *S*-oxides[6] to give the corresponding monosubstituted sulfines under very mild reaction conditions (–50 °C, 10 min), which thus allowed their isolation and purification. At the same time, we examined[2] the stereochemical course of the reaction of DMB with (*Z*)-phenyl- (**1a**) and (*Z*)-4-(methylphenyl)-sulfine (**1b**) (>98% isomerically pure), which gave diastereomeric mixtures of the corresponding *cis*- and *trans*-dihydrothiopyran *S*-oxides. The behavior of these monoaryl sulfines, which deviated from that of their unsymmetrically disubstituted analogues[3a,f] prompted us to perform a more detailed investigation of the stereochemical course of their cycloaddition. DMB and buta-1,3-diene (B) served as the diene reactants. At the same time, we explored the possibility that the reaction of less reactive dienes, like *cis*- and *trans*-penta-1,3-diene (*cis*- and *trans*-**3**), could be induced by catalysts.

Scheme I. Synthesis of *cis*- and *trans*-5,6-Dihydro-3,4-dimethyl-2*H*-thiopyran *S*-Oxides 2a–e from 2,3-Dimethylbuta-1,3-diene and Sulfines 1a–e



R: a = C_6H_5, b = p-Me-C_6H_4, c = m-Cl-C_6H_4, d = 2,4,6-Me_3-C_6H_2, e = Me_3C

Results and Discussion

(A) Reaction of Thioaldehyde *S*-Oxides 1a–e with DMB. Compounds **1a–c**[1] were available as 99:1 *Z*/*E* mixtures. Compound **1d**[1] was available as the pure *Z* isomer and **1e** as a ca. 75:25 *Z*/*E* mixture.[1,7] The reaction of aromatic sulfines **1a–d** with DMB afforded mixtures of the corresponding *cis*- and *trans*-dihydrothiopyran *S*-oxides **2a–d** (Scheme I) and varying amounts of *cis*- and *trans*-stilbenes. The latter arose from the decomposition of the sulfines.[8] The formation of these undesired by-products could be almost totally suppressed by diluting the sulfine with the diene. Thus, with DMB as the solvent for the reaction, the yield of cycloadducts was nearly quantitative (Table I). On the other hand, the reaction of a 75:25 *Z*/*E* mixture of sulfines **1e** afforded only a modest (30–40%) amount of the S-oxide *trans*-**2e**. The reactivity displayed by the aromatic sulfines **1a–c** differed slightly as a function of dienophilicity (entries 3, 7, and 12, Table I). Steric factors played a more important role, because (*Z*)-(2,4,6-trimethylphenyl)sulfine (**1d**) was far less reactive (entry 15) than the other aromatic sulfines. Finally, no substantial difference in reactivity between the aliphatic **1e** (entry 17) and the aromatic compounds **1a–c** was found.

(i) Product Distribution in and the Stereochemical Outcome of the Reaction of Aromatic Sulfines 1a–d. Even when sulfines **1a–d** were more than 98% *Z* isomerically pure, the subsequent reaction gave cis/trans mixtures of the cycloadducts. The structures of sulfoxides *trans*- and *cis*-**2a** were assigned after comparing their ^1H NMR spectra to that of the corresponding sulfide.[2,9a] The ^1H

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(7) This sulfine has also been prepared by a different method. See: Block, E. *Tetrahedron Lett.* **1980**, *21*, 1277.

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Table II. ^{1}H NMR Chemical Shifts and Coupling Constants in $CDCl_3$ (C_6D_6) of H(5), H'(5), and H(6) of the Dihydrothiopyran *S*-Oxides 2a–d,f

compd	δ H(5)	^{J}H(5)–H(6) (Hz)	δ H'(5)	^{J}H'(5)–H(6) (Hz)	δ H(6)	Δδ H(6)
trans-**2a**	2.56	8.1	2.76	5.3	4.04 (3.73)	0.31
cis-**2a**	3.04	11.2	2.27	4.4	3.65 (3.11)	0.55
trans-**2b**	2.62	8.1	2.84	5.1	4.08 (3.72)	0.36
cis-**2b**	3.09	11.2	2.33	4.6	3.71 (3.13)	0.58
trans-**2c**	2.63	8.6	2.81	5.2	4.04 (3.58)	0.46
cis-**2c**	3.07	11.2	2.33	4.6	3.68 (2.92)	0.76
trans-**2d**	2.79	11.1	2.57	6.3	4.50 (4.42)	0.08
cis-**2d**	3.61	12.7	2.40	3.9	4.08 (3.82)	0.16
trans-**2f**	2.73	8.1	2.94	5.3	4.04 (3.73)	0.31
cis-**2f**	3.11	11.2	2.52	4.4	3.65 (3.10)	0.55

Table III. Effects of Solvent Polarity (Entries 1, 2), Added TBAF (Entries 3–6), and the *E*/*Z* Distribution of the Monoaryl Sulfines 1a,d (Entries 7–9) on the Reactivity of the Sulfines toward DMB and on the Product Composition

entry	sulfine (*Z*:*E*)	DMB/1	TBAF/1	product (2) cis/trans ratio	$t_{1/2}$ (h)	*T* (°C)	yield (%)
1[a]	**1a** (99:1)	87		30:70	30.0	25	54
2[b]	**1a** (99:1)	87		27:73	25.0	25	63
3[c]	**1d** (*Z*)	148		19:81	500.0	70	70
4[c]	**1d** (95:5)	148	0.33	10:90	<10.0	65	70
5[c]	**1a** (99:1)	49		45:55	26.0	25	75
6[c]	**1a** (99:1)	49	0.33	10:90	0.5	25	60
7	**1d** (*Z*)	230		20:80	350.0	70	85
8	**1d** (60:40)	230		trans[d]	3.0	54	40[e]
9	**1d** (60:40)	1257		trans[d]	3.0	54	60[e]

[a] In CCl_4 (14 ml). [b] In CH_3CN (14 ml). [c] In the presence of THF (THF/1 = 27.0). [d] Unreacted (*Z*)-**1d** was quantitatively recovered. [e] With respect to (*E*)-**1d**.

NMR signal of H(6) of the sulfoxide was shifted downfield (to δ 4.12) when the hydrogen atom was syn to the oxygen atom, as in *trans*-**2a** and upfield (to δ 3.75) when it was anti, as in *cis*-**2a**, with respect to the same signal in the spectrum of the corresponding sulfide (δ 3.98). This behavior was as expected for protons β to the oxygen atom of the S=O group in cyclic sulfoxides.[9b] The structures of *S*-oxides **2b–d** were assigned after comparing their spectra with those of *trans*- and *cis*-**2a**. Furthermore, aromatic solvent- and lanthanide-induced shifts (ASIS and LIS experiments, Table II) supported these assignments. LIS experiments with $Yb(FOD)_3$ and *trans*- and *cis*-**2b** showed that the greatest downfield shift was observed for the signal due to H(6) of *trans*-**2b**, which indicated that a syn relationship existed between H(6) and the oxygen atom to which the lanthanide reagent was coordinated. ASIS experiments with compounds **2a–d** showed that the greatest upfield shift was observed for H(6) of the cis isomers, which suggested that a syn relationship existed between H(6) and the solvent benzene molecule.[10]

It is worth noting that the signal due to H(6) of compounds *cis*-**2a–c** consisted of four sharp peaks with apparently two coupling constants, $J_{H(6)-H(5)}$ = 4.4–4.6 Hz and $J_{H(6)-H(5)}$ = 11.1–11.3 Hz. From these values, it was apparent that H(6) occupied a *pseudoaxial* position in the dihydrothiopyran ring, anti and gauche to H(5) and H'(5), whereas the aryl substituent occupied a *pseudoequatorial* position. With *trans*-**2a–c**, the signal due to H(6) appeared as a sharp AB quartet, with peak separations of 5.1–5.3 and 8.1–8.6 Hz, respectively. This indicated that H(6) occupied a gauche position relative to H(5) and that the aryl substituent occupied a pseudoaxial position. On the other hand, the spectra of compounds *cis*- and *trans*-**2d** featured two quartets for the H(6) proton signal, with $J_{H(6)-H(5)}$ = 3.9 Hz and $J_{H(6)-H'(5)}$ = 12.7 Hz for the cis isomer and $J_{H(6)-H(5)}$ = 6.5 Hz and $J_{H(6)-H'(5)}$ = 11.1 Hz for the trans isomer. These values suggested that a pseudoequatorial position was occupied by the aryl substituent in both isomers.

In an attempt to determine the reasons for the loss of stereoselectivity in the reactions, several reactions of compounds **1a–d** with DMB, which also served as the solvent, were performed. Thus, the yield of cycloadducts was almost quantitative. All the monoaromatic sulfines behaved similarly. Analysis by 200-MHz ^{1}H NMR of the reaction mixture revealed that the relative amounts of the two isomeric products depended upon the initial DMB/sulfine ratio (Table I) and that the relative amount of the cis cycloadducts **2a–d** increased when this ratio was increased.

Because it had already been demonstrated[2] that a cis/trans equilibration of the cycloadducts did not occur, the observed stereochemical outcome of the reaction may have been the consequence either of a step-by-step reaction involving the formation of a 1,4-zwitterion that could lose its stereochemical integrity prior to ring closure, or of a *Z* to *E* isomerization of the parent sulfines during the cycloaddition. Thus, it was believed that the effect of solvent polarity, both on the reactivity of the sulfines and the product stereochemistry, could offer evidence[11a] that would indicate the formation of a dipolar intermediate. For this reason, **1a** and DMB (DMB/**1a** = 87.0) were allowed to react in both CCl_4 and CH_3CN in two separate experiments (entries 1 and 2, respectively, Table III). The results showed that neither the stereochemical course of the reaction nor the reactivity of the sulfines was affected by the polarity of the solvent. However, the absence of a solvent effect could not be taken only as "negative evidence"[11b] for reaction by way of a concerted process. The results could also be explained by a pathway that

(9) (a) Baldwin, J. E.; Lopez, R. C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1029. (b) Kondo, K.; Negishi, A. *Tetrahedron* **1971**, *27*, 4821 and references therein.

(10) It has been established that benzene associates with the positive end of the dipole of a molecule. In the case at hand, benzene complexes with the sulfur atom of the *S*-oxide on the opposite side of the oxygen atom. A similar effect was observed by Zwanenburg[3a] with unsymmetrically disubstituted sulfines.

(11) For an account of the effect of the solvent on the stereoselectivity of Diels–Alder reactions, see, for example: (a) Lehr, R. E.; Marchand, P. A. *Pericyclic Reactions*; Lehr, R. E., Marchand, A. P., Eds.; Academic Press: New York, 1977; Vol. 2, p 1. (b) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

Table IV. Effect of TFA (Entries 2, 4) on the Reactivity of Sulfines 1a and 1d toward DMB and on the Product Distribution

entry	sulfine (1) (Z:E)	DMB/1	TFA/1	product ratio cis/trans (2d)	t (h)	T (°C)	yield (%)
1	1a (99:1)	230		90:10	80	25	95
2	1a (95:5)[a]	170	1.9	55:45	2	25	85
3	1d (Z)	230		20:80	530	70	60[b]
4	1d (60:40)[a]	30	2.7	*trans*-2d	14	25	75

[a] After equilibration with TFA. [b] 30% of the initial amount of (Z)-1d was recovered.

involved the formation of an apolar "tight" cisoid intermediate in which charge separation was minimized.[12]

Therefore, the second possibility was tested. In such a case, the rate of formation of the trans cycloadduct would be regulated by the rate of the unimolecular Z to E isomerization. This isomerization would be competitive, especially at a low diene/sulfine ratio, with the bimolecular process of cycloaddition and would then lead to the stereospecific formation of the cis cycloadduct. However, careful monitoring by ^1H NMR spectroscopy during the course of the reactions revealed that the cis/trans product ratio remained stable. At the same time, no detectable build-up of E-sulfines **1a–d** was observed. Hence, the apparent loss of stereoselectivity could have arisen from the presence of a stable and almost undetectable amount of E-sulfine, which would react 2–3 orders of magnitude faster than the Z-sulfine. This interpretation, however, did not appear to be consistent with the observation that, for the concerted cycloaddition of unsymmetrically disubstituted sulfines to 1,3-dienes, the relative rate of reaction of the Z isomer was 10 times that of the E isomer.[3f]

Nevertheless, that the reaction proceeded in this manner was demonstrated by additional experimental evidence. In particular, previous studies[1] showed that tetra-*n*-butylammonium fluoride (TBAF) induced a rapid (a few minutes, 25 °C) Z/E equilibration of sulfines **1a–d**. For example, (Z)-**1d** was converted into a 95:5 Z/E mixture in this manner. So, the reactivities displayed by compounds (Z)-**1d** and -**1a** (Z/E = 99:1) toward DMB in the presence and absence of TBAF was compared. The presence of TBAF increased both the reactivity displayed by the sulfine and the relative amount of the trans cycloadduct produced (entries 4 and 6 compared to 3 and 5, Table III). This change was due to the presence of a steady-state concentration of the more reactive E-sulfine generated by TBAF.[13]

The striking differences in the reactivities of the E- and Z-monoaryl sulfines **1a-d** toward DMB became more evident after it was discovered[1] that strong Lewis acids, like $BF_3{\cdot}Et_2O$ and trifluoroacetic acid (TFA), induced the Z/E interconversion to a greater degree than did TBAF. For instance, the addition of a 10-fold molar excess of TFA to a CCl_4 solution of (Z)-**1d** gave, after a few hours at 25 °C, a 60:40 Z/E equilibrium mixture. Therefore, the reactivity of pure (Z)-**1d** (entry 7, Table III) could be compared to that of (E)-**1d**, present as the minor component of a 40:60 mixture after TFA was removed by extraction with water[1] (entries 8, 9). The results of these last two experiments showed that the trans cycloadduct was generated exclusively from the sulfine (E)-**1d** and not from (Z)-**1d**, which could be recovered quantitatively as soon as (E)-**1d** had disappeared. This result demonstrated that the rate of reaction of (E)-**1d** was ~3 orders of magnitude greater than that of (Z)-**1d** (entries 8 and 9 compared to 7). Finally, the yield of the cycloadduct (E)-**2d** could be increased by diluting the sulfine with the diene (entry 9 vs 8).

Chart I. *trans*- and *cis*-Phenyl-5,6-dihydro-2*H*-thiopyran *S*-Oxides 2f

Cis-2f *Trans*-2f

(ii) Product Distribution in and Stereochemical Outcome of the Reaction of the Aliphatic Sulfine 1e. The cycloaddition of the aliphatic sulfine **1e** to DMB afforded exclusively the S-oxide *trans*-**2e** (Table I, entries 16 and 17). The spectra of *trans*-**2e** fit those of the product obtained from the oxidation of 3,4-dimethyl-6-*tert*-butyl-5,6-dihydro-2*H*-thiopyran. The oxidation product had been assigned[14] the cis structure. But, after reexamination of the spectra the correct trans structure was assigned.[15] No detailed information bearing on the mechanism of cycloaddition was obtained from kinetic experiments performed with excess of diene as the solvent, due to the comparatively low yields of cycloadduct. However, the two isomeric sulfines (Z)- and (E)-**1e** disappeared at the same rate, which suggested that the selective formation of *trans*-**2e** was due to both a Z to E conversion and an extremely slow rate of cycloaddition, verging on inertness, of (Z)-**1e** to yield the corresponding diastereomer *cis*-**2e**. A similar steric effect was observed with (Z)-**1d** (see (i)).

(B) Reaction of Sulfine 1a and Buta-1,3-diene (B). A loss of stereoselectivity was also observed when sulfine **1a** (Z:E = 99:1) was allowed to react with B at 25 °C in CCl_4 solution saturated with B. A 1:1.6 mixture of the cis/trans S-oxides **2f** (Chart I) was obtained in 75% yield. The important spectroscopic characteristics of the cycloadducts, which were fully consistent with the assigned structures of compounds **2a–d**, are reported in Table II.

(C) Effect of Lewis Acid Catalyst. Lewis acid catalysts accelerate certain Diels–Alder reactions. The model proposed by Houk[16] for the reactions of α,β-unsaturated carbonyl compounds explains the role of this type of catalyst. In sulfine chemistry, the formation of charge transfer complexes from sulfines and Lewis acids, like H_2SO_4,[17] $BF_3{\cdot}Et_2O$,[1] and TFA,[1] has been experimentally confirmed. The coordination of the Lewis acid to the nonbonding electrons of the sulfine oxygen increases the electrophilicity of the sulfine[3a] by lowering the LUMO energy. Because no attempts to induce the cycloaddition of sulfines to dienes by Lewis acid catalysis have apparently been reported, the possibility that reactions between the thioaldehyde S-oxides **2a** and **2d** and DMB could be catalyzed by TFA was investigated. The results are

(12) For selected examples of step-by-step reactions involving apolar intermediates, see: Bartlett, P. D. *Science* **1968**, *159*, 833.

(13) Due to the presence of a steady-state concentration of the E-sulfine, the relative amount of the corresponding stilbene that was produced increased slightly when the reaction was performed in the presence of TBAF.

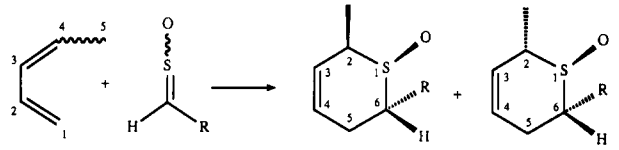
(14) The oxidation of the sulfide afforded a cis/trans mixture of the S-oxides **2e**, from which the pure trans isomer could be isolated by flash chromatography. See: Bonini, B. F.; Maccagnani, G.; Mazzanti, P.; Zani, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2083.

(15) Barbarella, G.; Bongini, A., Bonini, B. F.; Zambianchi, M.; Zani, P. To be published.

(16) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *92*, 4094.

(17) Carlsen, L.; Holm, A. *Acta Chem. Scand.* **1976**, *B30*, 277.

Scheme II. Regiospecific Formation of *cis*-2-Methyl- (4) and *trans*-2-Methyl-*trans*-6-mesityl-5,6-dihydro-2*H*-thiopyran *S*-Oxide (5) from *trans*-1,3-Pentadiene (3-*trans*) and *E*-Mesitylsulfine 1d



presented in Table IV. Sulfines **1a** and **1d** were equilibrated[1] to 95:5 and 60:40 *Z*/*E* mixtures, respectively, by treatment with TFA (entries 2 and 4, Table IV). Then, DMB was added. The rates of reaction were much greater than those of the uncatalyzed reactions. At the same time, the relative amounts of the *trans*-thiopyran *S*-oxides **2a** and **2d** that were produced increased[18] (entries 1, 2 and 3, 4). The hypothesis that TFA increased the overall rate of cycloaddition, not only by accelerating the conversion of the less reactive *Z*-sulfine isomer to the more reactive *E* isomer but also by increasing the dienophilicity of both isomers, was rigorously proven (entries 1 and 2). The rapid formation (within 2 h) of *cis*-**2a** as the major product of cycloaddition in the presence of TFA demonstrated that a considerable enhancement of the reactivity of the less reactive *Z*-sulfine also occurred.

Finally, the catalytic role of TFA in the reaction of sulfine **1e** (*Z*:*E* = 75:25) with DMB was studied. The presence of TFA (TFA:**1e** = 5:1) led to rapid interconversion of the sulfines. After a few minutes, a 40:60 *Z*/*E* equilibrium mixture was produced. In the subsequent reaction, the rates of disappearance of both sulfines increased. However, the formation of even a trace amount of the corresponding cis cycloadduct was not observed, and the yield of *trans*-**2e** decreased.

(D) Reaction of Sulfine 1d with *trans*- and *cis*-1,3-Pentadiene (*trans*- and *cis*-3). To gain more information on the effects of Lewis acid catalysis on these reactions, the reaction of the relatively unreactive *trans*-1,3-pentadiene (*trans*-**3**) with the sterically hindered sulfine (*Z*)-**1d** was studied. Preliminary experiments showed that no reaction occurred even at 100 °C. The presence of TBAF, which generated the more reactive (*E*)-**1d** from (*Z*)-**1d**, failed to induce cycloaddition. However, in the presence of TFA (TFA:**1d** = 1.2:1), a 60:40 *Z*/*E* mixture of **1d** and *trans*-**3** (**1d**:*trans*-**3** = 1:24) gave a 5:1 mixture of the diastereomeric S-oxides *cis*-2-methyl-*trans*-6-(2,4,6-trimethylphenyl)-2,6-dihydrothiopyran *S*-oxide (**4**) and its trans 2-isomer (**5**) (Scheme II) in 56% yield. Sulfoxides **4** and **5** gave satisfactory elemental analyses, and their spectra were consistent with their assigned structures. The relative configurations were established from the results of LIS and ASIS experiments (see Experimental Section). These experiments showed that in both isomers a syn relationship existed between the proton at C(6) and the oxygen atom, and that the two isomers were epimeric about the C(2) atom. That is, in the major isomer **4** a syn relationship existed between the oxygen atom and the C_2 methyl group, whereas in the minor isomer **5** the relationship was anti. This observation suggested that both isomers were formed from (*E*)-**1d** via a regioselective attack of the carbon atom of the sulfine C–S bond on the unsubstituted terminal carbon atom of the diene. The formation of the two isomers cannot be explained by a TFA-promoted isomerization either of the diene reactant or of the reaction products.[19] In fact, the isomerization of *trans*-**3** to *cis*-**3**, which should eventually lead to the stereospecific formation of sulfoxide **5**, did not occur in the presence of TFA. In contrast, the isomerization of *cis*-**3** to the thermodynamically more stable *trans*-**3** was observed when (*E*)-**1d** was allowed to react with *cis*-**3** under the reaction conditions described previously (TFA:**1d** = 1.2:1, **1d**:*cis*-**3** = 1:24). Significantly, the same 5:1 mixture of **4** and **5** was produced, but in substantially lower yield (30%). Thus, the observed product stereochemistry could have been produced either by an acid-induced step-by-step cycloaddition or by a reaction that proceeded through two Diels–Alder transition states, one that produced **4** (the "exo" product) and another that produced **5** (the "endo" product).

Conclusions

Two important observations were made in this study. First, the lack of stereospecificity in the cycloaddition of monoaryl sulfines to B and DMB was a result of a *Z*/*E* interconversion of the parent sulfine during the reaction. Second, a surprisingly high reactivity of the (*E*)-thioaldehyde *S*-oxides, compared to the *Z* isomers, was observed. A possible explanation for this behavior, which deviates from that of the unsymmetrically disubstituted sulfines, is that a large energy difference exists between the ground states of the two isomers. With both monoalkyl and monoaryl sulfines, the *Z* isomer was always the major component of a *Z*/*E* mixture. For alkyl sulfines, this preference for the *Z* form has been attributed to the existence of a "syn effect",[20] which stabilizes the *Z* form by σ and π bonding interactions between the hydrogen atoms of the alkyl group and the oxygen atom. For monoaryl sulfines, a stabilizing attraction between the partially positively charged *o*-H and the partially negatively charged oxygen atom should be present in the *Z* form.[1] As a consequence, the energy of activation for cycloaddition of an *E*-sulfine to a diene should be lower than that of its *Z* isomer.

Finally, the absence of a solvent effect (entries 1 and 2, Table III), was fully consistent with the observations of Zwanenburg and suggested that the uncatalyzed cycloaddition was a concerted process.

Experimental Section

General Procedure for the Synthesis of the Dihydrothiopyran *S*-Oxides 2a–d. A mixture of the sulfine and the diene was sealed in a vial under argon and was heated. Reaction temperatures and reaction times are given in Table I. Excess diene and the solvent were then evaporated at 25 °C under reduced pressure. The product trans/cis isomer ratio was determined by ^{1}H NMR analysis. The products were separated by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2 (2:8), unless otherwise stated). Other reaction conditions, product yields, and trans/cis isomer distributions of sulfoxides **2a–d** are also given in Table I. For the MS, IR, ^{1}H NMR, and ^{13}C NMR data for *trans*- and *cis*-**2b–d** and for the results of LIS experiments performed with compounds **4** and **5**, see the supplementary material.

Typical Procedure for the Cycloaddition. *cis*- and *trans*-6-Phenyl-3,4-dimethyl-5,6-dihydro-2*H*-thiopyran *S*-Oxides (*cis*-2a and *trans*-2a). Sulfine **1a** (0.048 g, 0.35 mmol) was allowed to react with DMB (0.55 mL, 4.80 mmol) at 25 °C

(18) Independent experiments showed that the *trans*- and *cis*-thiopyran *S*-oxides **2a–d** were not interconverted in the presence of TFA after several days at 70 °C.

(19) No epimerization was observed when the pure cycloadducts **4** and **5** were treated with TFA under the reaction conditions employed for the cycloaddition.

(20) Block, E.; Penn, R. E.; Bazzi, A.; Cremer, D. *Tetrahedron Lett.* **1981**, *22*, 29. Restricted Hartree–Fock calculations performed on ethanethioaldehyde *S*-oxide showed that the *Z* isomer was more stable than the *E* isomer by 1.8 kcal/mol.

for 3 days. Flash chromatography of the crude residue gave, in order, *cis*- and *trans*-**2a**. *cis*-**2a** (0.040 g, 0.183 mmol, 52.3%): mp 130–132 °C (ethyl ether/pentane); ^{1}H NMR ($CDCl_3$) δ 1.65–1.75 (b, 6 H, 2 Me), 2.27 (m, 1 H, H(5), $J_{H(5)-H'(5)}$ = 18.1 Hz, $J_{H(5)-H(6)}$ = 4.4 Hz), 3.04 (m, 1 H, H'(5), $J_{H'(5)-H(6)}$ = 11.2 Hz), 3.14 (m, 1 H, H(2), $J_{H(2)-H'(2)}$ = 17.3 Hz), 3.26 (m, 1 H, H'(2)), 3.65 (dd, 1 H, H(6)), 7.2–7.4 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) δ 19.66 (Me), 19.9 (Me), 30.1 (CH_2), 52.0 (CH_2), 57.8 (CH), 115.6 (C), 127.85 (C), 128.25 (3 CH), 128.8 (2 CH), 136.91 (C); IR (CS_2) 1045 (SO) cm^{-1}; MS *m/e* 220 (M^+), 171, 157, 143, 129. Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 70.61; H, 7.27; S, 14.65. *trans*-**2a** (0.024 g, 0.109 mmol, 31.1%): mp 85–87 °C (ethyl ether/pentane); ^{1}H NMR ($CDCl_3$) δ 1.65–1.75 (b, 6 H, 2 Me), 2.56 (m, 1 H, H(5), $J_{H(5)-H'(5)}$ = 19.0 Hz, $J_{H(5)-H(6)}$ = 8.1 Hz), 2.78 (m, 1 H, H'(5), $J_{H'(5)-H(6)}$ = 5.3 Hz), 3.10–3.34 (m, 2 H(2)), 4.04 (m, 1 H, H(6)), 7.2–7.4 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) δ 19.44 (Me), 34.12 (CH_2), 51.98 (CH_2), 62.24 (CH), 117.50 (C), 127.41 (C), 128.17 (2 CH), 128.41 (CH), 129.06 (2 CH), 135.2 (C); IR (CS_2) 1050 (SO) cm^{-1}; MS *m/e* 220 (M^+), 171, 157, 143. Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 70.60; H, 7.36; S, 14.72.

Reaction of Sulfine 1a with DMB in the Presence and Absence of TBAF. $TBAF{\cdot}3H_2O$ (0.0346 mmol in 0.12 mL of THF), **1a** (0.0146 g, 0.106 mmol, *Z*:*E* = 99:1) and DMB (0.421 g, 5.13 mmol, DMB:**1a** = 48.6) were placed in a ^{1}H NMR tube. The disappearance of the sulfine was followed by ^{1}H NMR spectroscopy. The reaction had a half-life of 32 min. A 10:90 mixture of *cis*- and *trans*-**2a** (0.014 g, 0.636 mmol, 60.0%) was obtained. The same reaction in the absence of TBAF had a half-life of 1600 min. A 45:55 mixture of *cis*- and *trans*-**2a** (0.0175 g, 0.795 mmol, 75%) was obtained.

Selective Reaction of Sulfine (*E*)-1d, in a 60:40 *Z*/*E* Mixture, with DMB. *Z*-**1d** (0.031 g, 0.172 mmol), in $CDCl_3$ (1 mL), was equilibrated at 25 °C to yield a 60:40 *Z*/*E* mixture after 3 h by treatment with TFA (0.15 mL, 0.235 g, 0.21 mmol). TFA was removed as described in ref 1, and then DMB was added (6.5 g, 76.65 mmol, DMB:**2d** = 1257). The solution was heated at 54 °C for 3 h. The mixture was purified by flash chromatography on silica gel (CH_2Cl_2, then ethyl acetate/CH_2Cl_2 (1:2)). Eluted, in order, were *trans*-2,2',4,4',6,6'-hexamethylstilbene[21] (0.008 g, 0.03 mmol, 18.0%), sulfine (*Z*)-**1d** (0.015 g, 0.83 mmol, 48.4%), mesityl aldehyde (0.018 g, 0.012 mmol, 7.0%), and *trans*-**2d** (0.0107 g, 0.406 mmol, 24.0%).

Reaction of Sulfine 1e and DMB. Sulfine **1e** (0.118 g, 1.0 mmol, *Z*:*E* = 75:25) was allowed to react with DMB (20 mL, 175.6 mmol, DMB:**2e** = 176) at 25 °C for 3 days. The ^{1}H NMR spectrum ($CDCl_3$) of the crude product mixture revealed the presence of the ***trans*-3,4-dimethyl-6-*tert*-butyl-5,6-dihydro-2*H*-thiopyran *S*-oxide** (*trans*-**2e**), which was isolated (0.085 g, 4.2 mmol, 42%) by flash chromatography on silica gel (CH_2Cl_2/ethyl acetate (10:3)). In another experiment, sulfine **1e** (0.10 g, 0.85 mmol, *Z*:*E* = 75:25) and DMB (1.0 g, 12.2 mmol, DMB:**2e** = 14.4) gave *trans*-**2e** (0.04 g, 0.2 mmol, 25%): mp 64–66 °C (pentane), ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9 H, 3 Me), 1.75 (br, 6 H, 2 Me), 2.39 (dd, 2 H(5)), 2.60 (dd, 1 H, H(6), $J_{H(5)-H(6)}$ = 10 Hz, $J_{H'(5)-H(6)}$ = 5.0 Hz), 3.4 (d, 2 H(2)). Other spectroscopic data for *trans*-**2e** are given in ref 15.

Reaction of Sulfine 1a and Buta-1,3-diene. A solution of sulfine **1a** (0.14 g, 1.01 mmol, *E*:*Z* = 99:1) in CCl_4 (20 mL) was saturated with buta-1,3-diene. The reaction mixture was allowed to stand for 10 days at 25 °C. The ^{1}H NMR spectrum of the crude product mixture showed the presence of the corresponding dihydrothiopyran *S*-oxides **2f** (cis:trans = 1.6:1). TLC (three developments on silica gel plates, with ethyl acetate) followed by extraction of the plates with methanol afforded, from the more mobile fraction, ***cis*-6-phenyl-5,6-dihydro-2*H*-thiopyran *S*-oxide** (*cis*-**2f**) (0.055 g, 0.29 mmol, 28.9%): mp 75–77 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 2.5 (m, 1 H, H(5)), 3.0–3.2 (m, 1 H, H'(5)), 3.3–3.4 (m, 2 H(2)), 3.74 (dd, 1 H, $J_{H(5)-H(6)}$ = 4.5 Hz, $J_{H'(5)-H(6)}$ = 10.8 Hz), 5.65 (m, 1 H), 6.05 (m, 1 H), 7.3–7.4 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) δ 29.99 (CH_2), 46.73 (CH_2), 57.49 (CH), 116.13 (CH), 128.28 (2 CH), 128.43 (CH), 128.86 (3 CH), 136.78 (C); IR (CS_2) 1045 (SO) cm^{-1}; MS *m/e* 192 (M^+), 176, 143. Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; S, 16.68. Found: C, 68.93; H, 6.25; S, 16.73. The less mobile fraction contained ***trans*-6-phenyl-5,6-dihydro-2*H*-thiopyran *S*-oxide** (*trans*-**2f**) (0.089 g, 0.47 mmol, 46.8%): mp 135–138 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 2.84 (m, 2 H(5)), 3.38 (m, 2 H(2)), 4.13 (dd, 1 H, $J_{H'(5)-H(6)}$ = 5.3 Hz, $J_{H(5)-H(6)}$ = 8.0 Hz), 5.6 (m, 1 H), 6.0 (m, 1 H), 7.3–7.4 (m, 5 H, arom); ^{13}C NMR ($CDCl_3$) δ 27.92 (CH_2), 46.78 (CH_2), 61.83 (CH), 117.84 (CH), 128.39 (2 CH), 128.66 (CH), 128.97 (CH), 129.94 (2 CH), 135.24 (C); IR (CS_2) 1055 (SO) cm^{-1}; MS *m/e* 192 (M^+), 176, 143. Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; S, 16.68. Found: C, 68.93; H, 6.25; S, 16.73.

Reaction of Sulfines 1a–e with DMB in the Presence of TFA. General Procedure. Solution of the *Z* and *E* isomers of the sulfine in CCl_4 was equilibrated in the presence of TFA. When equilibrium was established, DMB was added. The progress of the subsequent reaction was monitored by TLC. After the sulfine had disappeared, the solvent and excess DMB were evaporated. Workup of the residue with 5% aqueous $NaHCO_3$ and extraction with CH_2Cl_2 afforded a cis/trans mixture of the cycloadducts. The reactions of **1a** and **1e**, described in the following text, are typical.

Reaction of 1a and DMB in the Presence of TFA. TFA (0.16 g, 1.38 mmol) converted, in a few minutes, a 99:1 *Z*/*E* mixture of **1a** (0.10 g, 0.725 mmol, in 2 mL of CCl_4) to a 95:5 *Z*/*E* mixture. The reaction with DMB (11.0 g, 136.0 mmol, DMB/**1a** = 170) at 25 °C afforded, after 2 h, the *cis*- and *trans*-**2a** (0.136 g, 0.62 mmol, 85%, cis:trans = 55:45).

Reaction of 1e and DMB in the Presence of TFA. TFA (0.28 g, 2.4 mmol) and **1e** (0.095 g, 0.80 mmol, *Z*:*E* = 78:22) in CCl_4 (2 mL) gave a 40:60 *Z*/*E* mixture in a few minutes. The reaction with DMB (5.0 g, 61.0 mmol, DMB/**1e** = 76.3) afforded only *trans*-**2e** (0.034 g, 0.17 mmol, 21.3%).

Reaction of Sulfine 1d and *trans*- (*trans*-3) and *cis*-1,3-Pentadiene (*cis*-3). Sulfine **1d** (0.30 g, 1.67 mmol) was allowed to react with *trans*- or *cis*-**3** (2.7 g, 39.8 mmol) in the presence of TFA (0.16 mL, 2.10 mmol) at 55 °C for 24 h. After workup, the ^{1}H NMR spectrum of the crude reaction mixture gave the ratio of the S-oxides **4** and **5**. The two were separated by flash chromatography on silica gel (benzene/ethyl acetate (3:2)). From the reaction of *trans*-**3** were obtained 0.232 g (0.934 mmol, 56%) of **4** and 0.0464 g (0.19 mmol, 11%) of **5**. From the reaction of *cis*-**3** were obtained 0.124 g (0.50 mmol, 30%) of **4** and 0.025 g (0.10 mmol, 6%) of **5**. ***cis*-2-Methyl-*trans*-6-(2,4,6-trimethylphenyl)-5,6-dihydro-2*H*-thiopyran *S*-oxide (4)**: mp 116–118 °C (ethyl ether/pentane); ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3 H, 2 Me, *J* = 6.9 Hz), 2.2 (s, 3 H, Me), 2.3–2.6 (b, 6 H, 2 Me), 2.5–2.6 (m, 1 H, H(5), $J_{H(5)-H(6)}$ = 5.6 Hz), 2.87 (dd, 1 H, H'(5), $J_{H(5)-H'(5)}$ = 19.4 Hz, $J_{H(5H-H(6)}$ = 11.1 Hz), 3.77 (m, 1 H, H(2)), 4.62 (q, 1 H, H(6)), 5.8 (q, 2 H, H(3) and H(4), *J* = 10.6 Hz), 6.85 (b, 2 H, arom); ^{1}H NMR (C_6D_6) δ 1.32 (d, 3 H, Me, *J* = 7.1 Hz), 2.1 (s, 3 H, Me), 2.2–2.4 (b, 7 H, 2 Me and H(5)), 2.55 (m, 1 H, H'(5), $J_{H(5)-H'(5)}$ = 19.4 Hz, $J_{H'(5)-H(6)}$ = 11.2 Hz), 3.25 (m, 1 H, H(2)), 4.54 (q, 1 H, H(6), $J_{H(5)-H(6)}$ = 6.4 Hz), 5.3 (m, 2 H, H(3) and H(4)), 6.7 (b, 2 H, arom); ^{13}C NMR ($CDCl_3$) δ 10.83 (Me), 20.37 (Me), 20.91 (Me), 30.65 (CH_2), 49.52 (CH), 53.06 (CH); IR (CS_2) 1055 (SO) cm^{-1}; MS *m/e* 248 (M^+), 231, 189. Anal. Calcd for $C_{15}H_{20}OS$: C, 72.53; H, 8.11; S, 12.91. Found: C, 72.61; H, 8.07; S, 12.93.

***trans*-2-Methyl-*trans*-6-(2,4,6-trimethylphenyl)-5,6-dihydro-2*H*-thiopyran *S*-oxide (5)**: mp 142–144 °C (ethyl ether/pentane); ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3 H, Me, *J* = 7.3 Hz), 2.2 (s, 3 H, Me), 2.35 (s, 3 H, Me), 2.5 (s, 3 H, Me), 2.7 (m, 1 H, H(5), $J_{H(5)-H(6)}$ = 6.3 Hz), 2.9 (m, 1 H, H'(5), $J_{H'(5)-H(6)}$ = 11.2 Hz), 3.45 (m, 1 H, H(2)), 4.66 (m, 1 H, H(6)), 5.38 (m, 1 H, H(3)), 5.78 (m, 1 H, H(4)), 6.9 (b, 2 H, arom); ^{1}H NMR (C_6D_6) δ 1.34 (d, 3 H, Me, *J* = 7.6 Hz), 2.05 (s, 3 H, Me), 2.25 (s, 3 H, Me), 2.35 (s, 3 H, Me), 2.1–2.4 (m, 1 H, H(5)), 2.45–2.65 (m, 1 H, H'(5), $J_{H'(5)-H(6)}$ = 11.2 Hz), 3.20 (m, 1 H, H(2)), 4.66 (q, 1 H, H(6), $J_{H(5)-H(6)}$ = 6.3 Hz), 4.9 (m, 1 H, H(3)), 5.25 (m, 1 H, H(4)), 6.7 (b, 2 H, arom); ^{13}C NMR ($CDCl_3$) δ 16.06 (Me), 20.56 (Me), 21.46 (Me), 31.88 (CH_2), 57.99 (CH), 61.26 (CH); IR (CS_2) 1055 (SO) cm^{-1}; MS *m/e* 248 (M^+), 231, 189. Anal. Calcd for $C_{15}H_{20}OS$: C, 72.53; H, 8.11; S, 12.91. Found: C, 72.41; H, 8.06; S, 12.87. The relative configurations of **4** and **5** were established by LIS experiments. $Eu(FOD)_3$ was added to $CDCl_3$ solution of **4** (or **5**), and the ^{1}H NMR spectrum was recorded. The values of the chemical shift of the signals due to the protons at C(2) and C(6) and the protons

(21) Muszkat, K. A.; Fischer, E. *J. Chem. Soc., B* **1967**, 662.

of the C(2) methyl group were noted. More $Eu(FOD)_3$ was added, and the spectrum was again recorded. This addition-recording sequence was performed a total of five times. The maximum mole ratio (σ) of $Eu(FOD)_3$ to **4** (or **5**) was 0.02. Plots of chemical shift differences ($\Delta\delta$, in ppm) against mole ratio (σ) were linear ($\Delta\delta = a + \rho\sigma$) and had correlation coefficients ≥0.999. The plots are shown in Figures 1, 2, and 3 of the supplementary material for the C(6) proton, the C(2) proton, and the C(2) methyl group protons, respectively. Compounds **4** and **5** showed a similar downfield shift of the signal due to the proton at C(6) (ρ = 1810 for **4** and ρ = 1904 for **5**). The extent of the shift was typical of a proton syn to the oxygen atom. Moreover, the signals of the proton at C(2) of **5** (ρ = 1516) and the methyl group protons at C(2) of **4** (ρ = 1090) showed a similar, but more pronounced, shift than those of the proton at C(2) of **4** (ρ = 845) and the methyl group protons at C(2) of **5** (ρ = 594). These data demonstrated that the two isomers were epimeric at C(2). In the major isomer **4** a syn relationship existed between the oxygen atom and the C(2) methyl group, whereas in the minor isomer **5** an anti relationship existed between these substituents. ASIS studies gave similar results.

Supplementary Material Available: Figures 1, 2, and 3 and tables of IR, MS, ^1H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) spectroscopic data for *trans*- and *cis*-thiopyran *S*-oxides (5 pages). Ordering information is given on any current masthead page.

$S_{RN}1$-Based Methodology for Synthesis of Naphthylquinolines and Naphthylisoquinolines[1]

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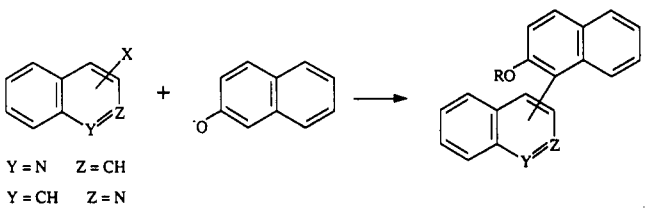
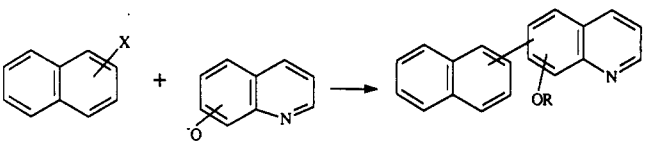
A versatile $S_{RN}1$ methodology allows straightforward access to title compounds via two strategies: (A) cross-coupling reactions of halobenzopyridine derivatives with anions from 2-naphthol or conversely of iodonaphthalene with anions from hydroxyquinoline and (B) total synthesis from either acetylchloropyridines in which the acetyl and chloro groups are ortho to each other or *o*-bromobenzamide treated with anions from acetonaphthone.

A research project in the field of bioorganic chemistry led us some time ago to devise a $S_{RN}1$ methodology[2] for synthesis of unsymmetrically substituted 2,2′-binaphthalene derivatives.[3a,b] To the best of our knowledge, no general method for synthesizing their aza analogues naphthylbenzopyridine derivatives (Figure 1) has been reported. The naphthylisoquinoline alkaloids encountered in Ancistrocladaceae have not been synthesized by direct methods like the classical Ullmann reaction, which has afforded only trace amounts of the mixed coupling product.[4] Moreover, there are only scattered reports in the literature on the preparation of this class of compounds.[5]

Scheme I



Scheme II



The synthesis of the related phenylpyridine derivatives[6-8a,b] could possibly be adapted to our purpose, but we considered that $S_{RN}1$ chemistry might provide easy and versatile access to naphthylquinoline and naphthylisoquinoline derivatives. Indeed, two direct routes appeared feasible: (A) regiospecific cross coupling between naphthyl and benzopyridyl moieties and (B) total synthesis from

(1) $S_{RN}1$ Studies. 26. Previous reports include the following: (a) Amatore, C.; Beugelmans, R.; Bois-Choussy, M.; Combellas, C.; Thiebault, A. *J. Org. Chem.* **1989**, *54*, 5688. (b) Symons, M. C. R.; Beugelmans, R.; Bowman, W. R.; Lechevallier, A. *Tetrahedron Lett.* **1989**, *30*, 5949. (c) Part 25: ref 3.

(2) Aromatic nucleophilic substitution reactions via chain radical mechanism ($S_{RN}1$) were discovered in 1970 by J. F. Bunnett and were investigated by his group and others since then. Those reactions require no strong activating groups, are compatible with many electron-withdrawing or -releasing substituents, and are regiospecific. An account was given by J. F. Bunnett (Acc. *Chem. Res.* **1978**, *11*, 413) and a general treatment by R. A. Rossi and R. H. de Rossi (*Aromatic Substitution by the $S_{RN}1$ Mechanism*; ACS Monograph 178; American Chemical Society: Washington, DC, 1983). For a review of synthetic extensions, see: Beugelmans, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 547.

(3) (a) Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *J. Org. Chem.* **1987**, *52*, 3880. (b) Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *Tetrahedron* **1989**, *45*, 4302.

(4) Bringman, G.; Jansen, J. R. *Tetrahedron Lett.* **1984**, *25*, 2537. For a review, see: Bringman, G. The Naphthylisoquinoline Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, Chapter 3, p 141. Photochemical mixed aryl coupling of the two molecular moieties prelinked by a benzyl ether bridge was the key step of the nonbiomimetic total synthesis of naphthylisoquinoline alkaloids (pp 173-181).

(5) Nelson, N. A.; Paquette, L. A. *J. Org. Chem.* **1962**, *27*, 964. Reacting 6-methoxy-2-tetralone with (6-ethoxy-2-pyridyl)lithium was the key step of the mixed coupling reaction.

(6) Akiba, K.-Y.; Yseki, Y.; Wada, M. *Tetrahedron Lett*, **1982**, *23*, 429 and references cited therein. The authors have found that $PhCuBF_3$ in THF was superior to other organometallic reagents for synthesis of 4-phenylpyridine from *N*-(ethoxycarbonyl)pyridinium chloride.

(7) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237 and references cited therein. The authors report that arylboronic acids were found to couple efficiently with 5-bromonicotinates to yield 5-arylnicotinates, but that the reaction was sensitive to steric inhibition in the arylboronic acid component.

(8) (a) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. (b) Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5097. 2-Arylpyridines and heteroterphenyl were obtained by Pd^0-catalyzed cross coupling of arylboronic acids with aryl bromides.

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