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1,3-CYCLOADDITIONS OF ALIPHATIC THIONE *S*-METHYLIDES TO DIMETHYL 2,3-DICYANOFUMARATE AND 2,3-DICYANOMALEATE; A TEST CASE FOR STERIC COURSE AND MECHANISM [1]

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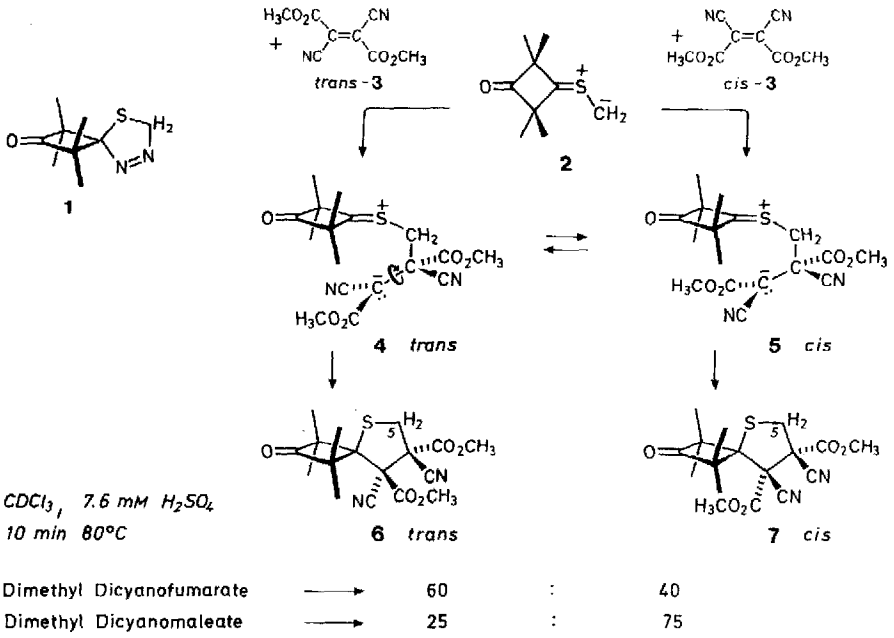
Summary The 1,3-cycloadditions of thione *S*-methylides 2 and 9 to dimethyl 2,3-dicyanofumarate and 2,3-dicyanomaleate are nonstereospecific. A preceding cis,trans isomerization of the unsaturated dipolarophiles catalyzed by the thiadiazolines (precursors of the thione *S*-methylides) had to be suppressed in order to clarify the stereochemical leakage *during* the cycloaddition.

The easily available spiro-1,3,4-thiadiazoline 1 [2] extrudes N_2 at 40°C in a 1,3-dipolar cycloreversion (THF, $t_{1/2}$ 87 min); the thione *S*-methylide 2 generated is interceptible *in situ*. We reported on the nonstereospecific addition of 2 to the C=C bond of 2,3-dicyanofumaric ester (trans-3) affording trans and cis-adduct, 6 and 7, in the ratio of 52:48 (THF, 8 h 40°C, 90%); [3] there was no evidence for the occurrence of cis-3. A great difference of the π-MO energies of the nucleophilic 1,3-dipole and the electrophilic dipolarophile as well as steric screening of *one* terminus of 2 were regarded as prerequisites for the unusual *two-step pathway* of 1,3-dipolar cycloaddition. The zwitterions 4 and 5 were proposed as attractive intermediates. [3,4] In contrast, the combination of 2 both with fumaronitrile and maleonitrile are stereospecific with >99.9%; these cycloadditions are probably *concerted*.

In 1986 Gotoh, Padias, and Hall [5] succeeded in preparing *dimethyl 2,3-dicyanomaleate* (cis-3) by isomerization of trans-3 photosensitized by 1 equiv of 1,4-dicyanobenzene. In our hands, the direct photoreaction in CH_2Cl_2 in an acid-washed duran reactor (high-pressure mercury arc) proved more convenient, sparing us the separation of the sensitizer. The irradiated solution contained cis-3/trans-3 = 91:9 and allowed the crystallization of 86% cis-3 with <2% trans-3. Several recrystallizations were required to diminish the share of the less soluble trans-3 to ≤0.2%.

The ^{1}H NMR analysis was based on the OCH_3 singlets of trans-3 (δ 4.03) and cis-3 (3.94) in $CDCl_3$; comparison with the ^{13}C satellites of the major isomer in the high-field spectrum allowed quantitative determination of small percentages. Nucleophilic reagents like dispersed KF established an 88:12 trans, cis equilibrium of 3 ($CDCl_3$, 2 days).

It was observed that thiadiazoline 1 catalyzes a slow *cis,trans isomerization* of 3 at room temperature; not the thioether, but rather the cis azo group of 1 appears to be responsible. A configurational change of the dipola-



rophile 3 prior to the cycloaddition seriously interferes with the stereospecificity test. Indeed, after reacting 1 with 1.1 equiv of trans-3 or cis-3, the unconsumed 3 showed isomerization, little in the case of trans-3 and much for cis-3, due to the position of the equilibrium.

We noticed an inhibitory function of acids on the thiadiazoline catalysis. Optimal was 7.6 mM H_2SO_4 in $CDCl_3$ reproducibly obtained by shaking $CDCl_3$ [6] with 98% sulfuric acid and decanting after 2 days. 0.1 M Thiadiazoline 1 isomerized 0.12 M cis-3 in $CDCl_3$ within 250 min at 25°C to cis/trans = 81:19; a 98:2 ratio was observed in the presence of 7.6 mM H_2SO_4. A second trick further assisted in curbing the undesired catalysis. Thiadiazoline 1 enters into competing pathways: *bimolecular* catalysis of the isomerization cis-3 ⇌ trans-3 and *unimolecular* extrusion of N_2. Due to the negative $\Delta S^{\ddagger}$ of bimolecular reactions, the rate constant of the catalytic isomerization should rise less with increasing temperature than k_1 of the cycloreversion 1 → 2 + N_2.

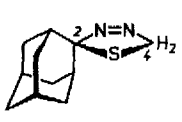
When 1 was reacted with 1.2 equiv of cis-3 in $CDCl_3$, 7.6 mM in H_2SO_4, for 10 min *at 80 °C*, the 360 MHz ^1H NMR spectrum indicated less than 1% trans-3 in the unconsumed cis-3; in contrast, after the reaction *at 40 °C* (10 h) the share of trans-3 was 10%. Due to fortunate analytical conditions, *several* isolated signals of thiolanes 6 and 7 were available for integration and comparison with weighed standards. The averaged ratios of trans and cis-thiolane observed in a series of experiments with trans-3 and cis-3 are shown in the formula scheme above. Thiolane yields were mostly 60-80%.

No isomerization, 6 ⇌ 7, was noticed even under drastic conditions, 7 d in benzonitrile at 139°C. Reactants and products being configurationally stable, the substantial loss of stereochemical integrity leaves no doubt: rotation must take place in intermediates - the zwitterions 4 and 5 are likely candidates - before the thiolane rings are closed. Rotational equilibrium is not attained, and the stereochemical leakage was greater for the trans-zwitterion 4 (40%) than for the cis-form 5 (25%). A competition experiment revealed that 2 combined with trans-3 4.6 times faster than with cis-3 ($CDCl_3$, 80°C).

The suppression of the preceding cis,trans isomerization of 3 at 80°C in the presence of H_2SO_4 rules out an alternative pathway: rotation in the zwitterion and *dissociation* back to the reactants. For entropy reasons, more dissociation would be expected at 80°C than at 40°C. However, less isomerization of cis-3 occurred at the higher temperature.

Diisopropyl 2,3-dicyanofumarate and 2,3-dicyanomaleate are less prone to the nucleophilic catalysis of the isomerization. In tests with 1 equiv of 1 in $CDCl_3$ at 25°C, no cis,trans isomerization of cis-3 was detected after 270 min, with and without added H_2SO_4. The advantages of lower sensitivity to nucleophiles and higher solubility are offset by analytical difficulties: the isopropyl signals of the cis,trans isomeric dipolarophiles overlap with those of the thiolanes, 6 and 7, $OCH(CH_3)_2$ instead of OCH_3, i.e., dicyanofumarate cannot be discerned in the unconsumed dicyanomaleate.

Reactions of 1 with the diisopropyl esters were run in $CDCl_3$, 7.6 M in H_2SO_4, for 10 min at 80°C, and integration of the 5-H_2 signals of the thiolanes provided the same trans,cis adduct ratios as the dimethyl esters 3: 61:39 starting from diisopropyl dicyanofumarate and 25:75 from the cis isomer.



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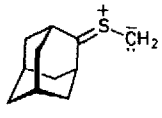

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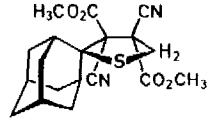
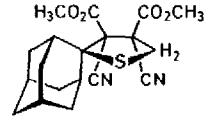


10 *trans*



11 *cis*

1,3,4-Thiadiazoline-2-spiro-2'-adamantane (8) generates 9 at 45°C.[7] According to our earlier report,[3] 9 added to trans-3 in THF furnishing trans and cis-thiolane, 10 and 11, in 59:41 ratio. Thiadiazoline 8 (0.1 M in $CDCl_3$) turned out to be a more active catalyst than 1 in the isomerization of cis-3 (0.11 M): after 250 min at 25°C, cis-3/trans-3 = 54:46 was measured; 73:27 in the presence of 7.6 mM H_2SO_4 testified to an insufficient protection.

In a series of experiments with 1.1 equiv of cis-3 (7.6 mM H_2SO_4) in $CDCl_3$, 10 min 80°C), the concentration of 8 was increased from 26 mM to 1540 mM in the expectation that a rising trans/cis thiolane ratio, 10/11, would re-

flect the increase of isomerization of 3 prior to the cycloaddition. Ratios of 10/11 from 14:86 to 31:69 were monitored, but the amount of trans-3 in the unconsumed cis-3 did not regularly increase with the concentration of 8. The best experiment exhibited only 11% cis→trans isomerization in the remaining cis-3, and the thiolane ratio of 14:86 was the smallest. A ratio of 10/11 = 72:28 in experiments with trans-3 appears even more trustworthy, since the equilibrium trans-3 ⇌ cis-3 harbors only 12% cis isomer, and trans-3 exceeds cis-3 in dipolarophilic activity.

With shares of 28% cis-thiolane 11 from trans-3 and 14% (or less) trans-thiolane 10 from cis-3, the cycloadditions of *S*-methylide 9 present more retention of dipolarophile configuration than those of 2. The interaction of 8 with the less sensitive diisopropyl esters confirmed the magnitude: 23% cis-thiolane from dicyanofumarate and 15% trans-thiolane from dicyanomaleate.

The mechanistic conclusions of the earlier report [3] remain untouched. Differences between thiocarbonyl ylides 2 and 9 in their steric course of cycloaddition can be explained either by different rate ratios of rotation and cyclization of the zwitterionic intermediates or by varying participation of a concerted pathway (retention). The stereospecific (> 99.6%) cycloaddition of thiobenzophenone *S*-methylide to trans-3 [8] may be remembered. However, the non-stereospecificity observed for some other aliphatic thione *S*-methylides [4] calls for reexamination; the losses of dipolarophile configuration *before* and *during* the cycloaddition need to be distinguished.

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