1,3-CYCLOADDITIONS OF 2,2,4,4-TETRAMETHYLCYCLOBUTANE-1-ONE-3-THIONE S-METHYLIDE

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Abstract – The 1,3,4-thiadiazoline 2, prepared from 2,2,4,4-tetra-methylcyclobutane-1-one-3-thione and diazomethane, loses N_2 at 40°C; the thiocarbonyl ylide 5 is a transient intermediate which *in situ* undergoes 1,3-dipolar cycloadditions to electron-deficient dipolarophiles with C≡C, C=C, C=S, C=O, and N=N bonds. Structures and mechanism are discussed.

Although simple aliphatic thioketones are known,[1,2] only the sterically hindered representatives are storable in the *monomeric* state. Their merciful inertness toward the human olfactory system contributes to the ease of handling.

In 1970 Diebert [3] reacted the red 2,2,4,4-tetramethylcyclobutane-1-one-3-thione (1)[4] with diazomethane and isolated 67% of the spirothiirane 3; the structure of the spiro-1,3,4-thiadiazoline (2) was assigned to an intermediate which was observed at 0°C as a white solid.
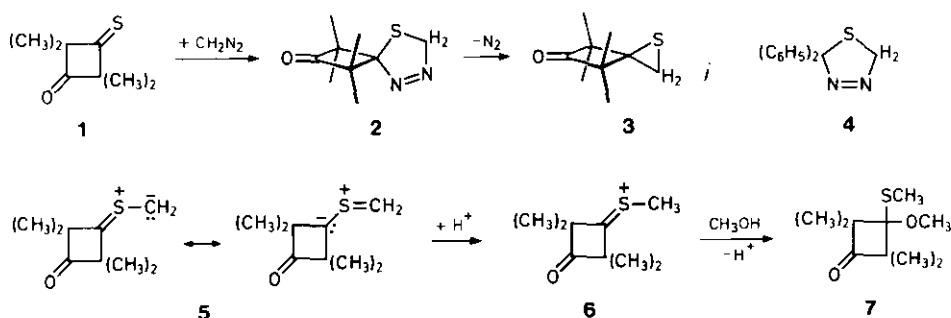
We passed gaseous diazomethane into 3 mmoles of 1 in 10 ml ether at -78°C, evaporated at 0°C and dissolved the crystalline residue in 10 ml pentane. After 30 min at

-78°C, 88% of the colorless $\underline{2}$ were filtered, mp 40-42°C (dec.); ^{1}H NMR (CDCl$_3$): δ = 1.23 (s, 2 CH$_3$), 1.31 (s, 2 CH$_3$), 5.84 (s, 5-H$_2$). Correct CH, N, S analyses of $\underline{2}$ were obtained. The N$_2$ extrusion of $\underline{2}$ obeyed first-order kinetics with $t_{1/2}$ = 25 min at *+45°C* in xylene, in agreement with Diebert's measurement ($t_{1/2}$ = 22 min at 49°C in CCl$_4$).[3] 2,2-Diphenyl-1,3,4-thiadiazoline ($\underline{4}$) loses N$_2$ with $t_{1/2}$ = 55 min in THF at *-45°C* [5] whereas 2,2,5-triphenyl-1,3,4-thiadiazoline decomposes at *-65°C* with $t_{1/2}$ ∿ 30 sec.[6] Thus, *alkylated* thiadiazolines are more stable than arylated ones.

The elimination of N$_2$ from $\underline{2}$ is a 1,3-dipolar cycloreversion and the thione *S*-methylide $\underline{5}$ the expected intermediate. The electrocyclization of the planar thiocarbonyl ylide system in $\underline{5}$ giving the thiirane $\underline{3}$ is accompanied by two 90° rotations about the CS bonds. Such processes require substantial activation energy because most of the resonance energy of $\underline{5}$ is sacrificed in the transition state. Experience shows that *intermolecular* interception by active dipolarophiles is usually faster. The pioneer work of Buter, Wassenaar, and Kellogg [7] demonstrated that thiocarbonyl ylides are involved in the N$_2$ extrusion from alkylated thiadiazolines. We have recently described 1,3-dipolar cycloadditions of adamantanethione *S*-methylide ($\underline{8}$), prepared in analogy to $\underline{5}$, to electron-deficient dipolarophiles with CC double and triple bond as well as CO and CS double bond.[8,9]

The thiocarbonyl ylide $\underline{5}$ is basic. When $\underline{2}$ was warmed in methanol with a drop of trifluoroacetic acid for 8 h at 40°C, ^{1}H NMR analysis indicated 80% of the O,S-dimethylacetal $\underline{7}$; mp near 20°C, ^{1}H NMR (CDCl$_3$): δ = 1.32 (s, 4 CH$_3$), 1.92 (s, SCH$_3$), 3.37 (s, OCH$_3$). The protonated species $\underline{6}$ is a logical intermediate and the CH$_2$ group of $\underline{5}$ is the more basic center among the two termini.

2,2,4,4-Tetramethylcyclobutane-1-one-3-thione *S*-methylide ($\underline{5}$) is an active 1,3-dipole despite a steric encumbrance at one terminus which by far exceeds that of $\underline{8}$. After warming pure $\underline{2}$ in THF in the presence of 1.1 equiv of dipolarophile for 8 h at 40°C, the evolution of N$_2$ was complete. The less active dimethyl acetylenedicarboxylate was used in excess as solvent. Quantitative ^{1}H NMR analysis (CDCl$_3$) by comparison with a weighed standard (1,1,2,2-tetrachloroethane) afforded the yields listed in Table 1. The isolated adducts were characterized by analyses and spectra.

The NMR spectra of the cycloadducts are reliable probes of symmetry or chirality, respectively. Adducts $\underline{9}$ and $\underline{10}$ show singlets for 5-H$_2$ and pairwise equivalence of the methyl signals: δ 1.25 and 1.42 for $\underline{9}$, 1.45 and 1.95 for $\underline{10}$. The ^{13}C NMR spec-

Table 1. Reactions of thiadiazoline $\underline{2}$ with dipolarophiles in THF
(8 h 40°C); adduct yields based on ^{1}H NMR analysis (isolation)

Dipolarophile	% adduct	mp (°C)	Formula
Dimethyl acetylenedicarboxylate	87	76-78	$\underline{9}$
Fumaronitrile	93	111-113	$\underline{11}$
Maleonitrile	92	140-142	$\underline{12}$
Maleic anhydride	(76)	207-209	$\underline{13}$
N-Phenylmaleimide	(76)	194-196	$\underline{14}$
Tetracyanoethylene	73	213-215	$\underline{10}$
trans-β-Nitrostyrene	72	121-123	$\underline{15}$
Thiobenzophenone	56	124-126	$\underline{17}$
	+ 23	(not isol.)	$\underline{18}$
Thioxanthione	(95)	174-177°	$\underline{19}/\underline{20}$
Adamantanethione	88	139-141	$\underline{21}$
2,2,4,4-Tetramethyl-cyclo- butane-1-one-3-thione	76	159-161	$\underline{22}$
Chloral	95	65-67	$\underline{24}$
Dimethyl azodicarboxylate	58	110-112	$\underline{25}$
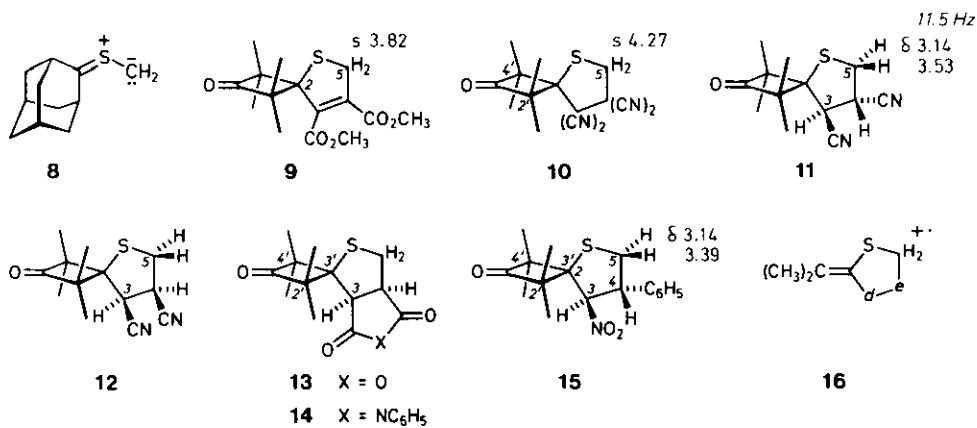
trum of $\underline{10}$ records δ 67.8 for C-2' + C-4', 22.9 and 22.7 for 4 CH_3 as well as 110.0
and 110.5 for 4 CN. Complex ABXY patterns appear in the ^{1}H NMR spectra of the chi-
ral adducts $\underline{11}$-$\underline{15}$, sometimes only the doublet of 3-H being resolved. All the methyl
groups are different, *e.g.*, δ 1.30, 1.42, 1.55, 1.65 for $\underline{11}$. In the ^{13}C NMR ($CDCl_3$)
of $\underline{13}$ the 4 CH_3 were observed and three singlets are assigned to C-2', C-3', and
C-4'.

trans-β-Nitrostyrene furnished only isomer 15 within the limits of the ^{1}H NMR spectrum. The doublet of 3-H at δ 5.45 - in contrast to δ(3-H) = 3.87 for 11 and 12 - leaves no doubt that the deshielding nitro group is located in 3-position. Thus, the CH_2 terminus of 5 is the more nucleophilic center.

The cycloadditions to fumaronitrile and maleonitrile proceed stereospecifically; within the ^{1}H NMR analytical limits no mutual admixture of 11 and 12 could be recognized. $J_{3,4}$ amounts to 2.3 Hz for 11 and 4.5 Hz for 12, compared with 3.0 Hz for 15 and 7.0, 6.2 Hz for 13 and 14.

The base peak of most mass spectra corresponds to $M^+- C_4H_6O$, *i.e.*, the elimination of dimethylketene provides radical cations 16. Also the peak of dimethylketene radical cation is present, and the ratio of the two peaks depends on the ionization potentials: 100:95 for 11, 100:90 for 12, 100:20 for 13, but 5:100 for the tetracyanoethylene adduct 10. The base peak of 15 is *m/e* 203 ($M^+- C_4H_6O - NO_2$) and the occurrence of *m/e* 104 (styrene[+], 35%) is in accordance with the addition direction.


17   18   19   20

21   22   23
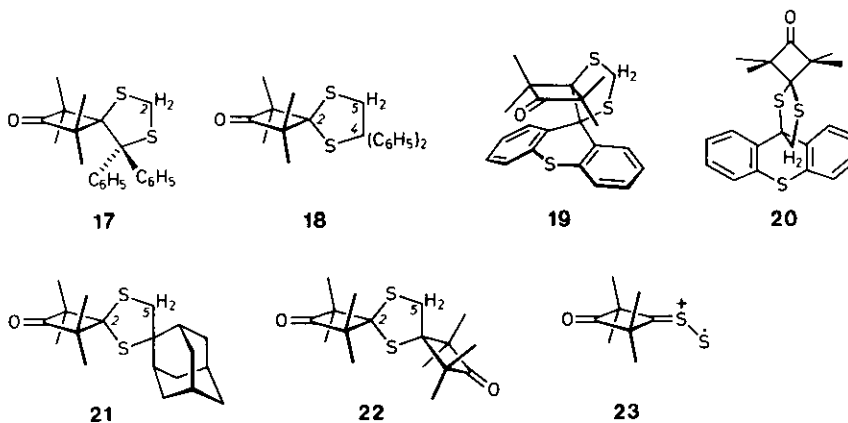
Both orientations were used by thiobenzophenone as a dipolarophile: 56% 17 and 23% 18. The minor product was enriched by thick-layer chromatography, but not obtained pure. The major product 17 likewise resulted from the reaction of thiobenzophenone *S*-methylide with the thione 1 (90%) at −45°C; this convergence proves the presence of -S-CH_2-S- in 17. Aromatic thione *S*-methylides always follow this course in their "Schönberg reactions" with dipolarophilic CS double bonds,[10,11] *i.e.*, the *type A* of the preceding communication.[9] Conceivably, it is steric hindrance which makes the *type B* addition - yielding 18 here - competitive. Structures 17 and 18 are confirmed by the ^{13}C NMR diagnostic criterion previously used.[9] δ(C-2) of 17 emerges at 25.3

and δ(C-5) of <u>18</u> at 50.0. The *corresponding* ^{1}H *NMR singlets appear at* δ *3.32 for*

2-H$_2$ of <u>17</u> and at 3.75 for 5-H$_2$ of <u>18</u>. A plane of symmetry reduces the number of

[1]H and ^{13}C signals for <u>17</u> and <u>18</u>.

Thioxanthione afforded a 5:1 mixture of <u>19</u> and <u>20</u> in high yield, but the separation

did not succeed. The ^{13}C triplets of 2-CH$_2$ (<u>19</u>) and 5-CH$_2$ (<u>20</u>) were found at δ 37.4

and 45.0. In the ^{1}H NMR spectrum the CH$_3$ pairs of <u>19</u> emerge at δ 0.79 and 1.24 whe-

reas those of <u>20</u> coincide at 1.31; the high-field absorption of <u>19</u> (0.79) reve-

als the shielding by the aromatic nuclei.

The addition of <u>5</u> to adamantanethione (88% <u>21</u>) and thione <u>1</u> (76% <u>22</u>) followed the

type B [9] pattern with its lower steric requirements. A diminished dipolarophilic

activity of <u>1</u> is concluded from the modest yield of <u>22</u> and the presence of 10% thi-

irane <u>3</u>. Diebert [3] isolated 31% of <u>22</u> when he treated thione <u>1</u> with 0.8 equiv diazo-

methane. The analogy with Schönberg's dithiolane formation [10] was recognized,[3] but

its mechanism was not yet understood at the time. The first 1,3-dithiolane of *ty-*

pe B was described in 1965 as a 2:1 product from hexafluorothioacetone and diazo-

methane (-78°C).[12]

[13]C triplets at δ 47.0 (<u>21</u>) and 43.4 (<u>22</u>) for C-5 mark both adducts as belonging

to *type B*. According to ^{1}H and ^{13}C NMR evidence, <u>22</u> and <u>21</u>, possesses *one* C_s plane,

i.e., the two cyclobutanone systems in the doubly spiro linked <u>22</u> are non-equivalent.

The mass spectra corroborate structures <u>21</u> and <u>22</u>. Besides the elimination of di-

methylketene (M$^+$- C$_4$H$_6$O), the fragmentation of <u>21</u> into C$_8$H$_{12}$S$_2$O$^+$ (15%) - probably

<u>23</u> - and C$_{11}$H$_{16}^+$ (2-methyleneadamantane, 15%) is indicative of *type B*.[9]

24   **25**
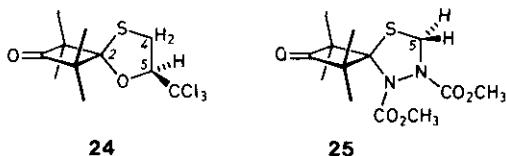
The expectation of structure <u>24</u> for the chloral adduct (95% yield) is confirmed

by the ABX spectrum of the 1,3-oxathiolane protons: dd of 5-H at δ 4.55. As foreseen,

small signals, *m/e* = 318 and 316, occur as parent peaks due to [37]Cl and [35]C isoto-

pes; *m/e* = 248 (85%) and 246 (85%) are the peaks for M$^+$- C$_4$H$_6$O whereas *m/e* = 70

(C$_4$H$_6$O$^+$) constitutes the base peak. The interaction of <u>2</u> with dimethyl azodicarbox-

ylate led to <u>25</u>. Its heteroring rests in a frozen non-planar conformation, as the

AB spectrum of the 5-H$_2$ (δ 4.38 and 4.58, J = 7.5 Hz) and the nonequivalence of the methyl groups (δ 1.27 for 2 CH$_3$, 1.40, 1.65) testify.

The synthetic potential of the cycloadditions of thiocarbonyl ylides goes beyond the preparation of 5-membered S-containing heterocycles. The easy removal of sulfur by CS hydrogenolysis recommends the reaction sequence as a method of CC linking of three units (thione, diazoalkane, dipolarophile).

We presume that a thermodynamic factor contributes to the superiority of the CS over the CO double bond as dipolarophile. The π bond which is sacrificed in the cycloaddition amounts to 94 kcal mol^{-1} for CO (ketones) and to 55–60 kcal mol^{-1} for CS; a portion of the difference may become effective in the transition state of the concerted cycloaddition.

ACKNOWLEDGMENT

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