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CHEMO- AND STEREOSELECTIVITY IN 1,3-DIPOLAR CYCLOADDITIONS OF THIOCARRBONYL YLIDES WITH A 1,4-METHANONAPHTHALENE-5,8-DIONE DERIVATIVE

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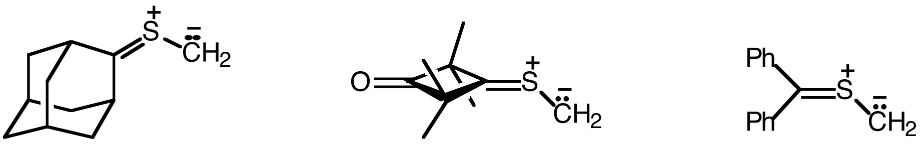
(Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday)

Abstract – The reaction of 1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (**2**) with aliphatic and aromatic thiocarbonyl ylides (**1a**-**c**) gave polycyclic tetrahydrothiophene derivatives (**5a**-**c**) by a chemo- and stereoselective 1,3-dipolar cycloaddition. The 1,3-dipoles (**1a**-**c**) were generated by thermal elimination of nitrogen from the corresponding 2,5-dihydro-1,3,4-thiadiazoles (**4a**-**c**).

INTRODUCTION

Recently, 1,3-dipolar cycloadditions of *in situ* generated thiocarbonyl ylides with C,C multiple bonds were reported as efficient and convenient approaches for the synthesis of thiophene derivatives.[1,2] According to general rules of cycloaddition processes,[3] electron-rich thiocarbonyl ylides smoothly react with electron-poor C,C dipolarophiles. In the case of dimethyl 1,2-dicyanofumarate, the cycloaddition does not follow the concerted pathway, and a mixture of two isomeric tetrahydrothiophenes was obtained.[4] This result indicated that extremely electron deficient alkenes may react in a stepwise manner. On the other hand, non-activated alkenes and alkynes such as cyclohexene and phenylacetylene were unreactive towards adamantanethione *S*-methylide (**1a**)[5] and 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide (**1b**), respectively.[6] Similar reactivity was reported for thiobenzophenone *S*-methylide (**1c**).[7,8] Strained cyclic systems are sufficiently reactive to intercept thiocarbonyl ylides, as shown in reactions with (*E*)-cyclooctene[9] and cyclooctyne.[6]

Formulae **1a-c**

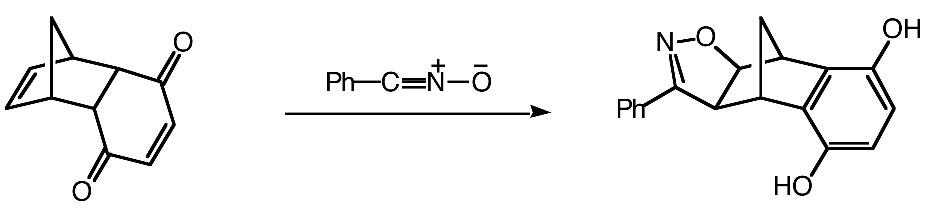


1a **1b** **1c**

In contrast to [3+2] cycloadditions of various 1,3-dipolar species (e.g. nitrile ylides,[10,11] nitrile oxides,[12-14] nitrile imides,[13,15] nitrones,[12,16] azomethine ylides,[17,18] and diazo compounds[19,20]), the chemoselectivity (site selectivity) of additions with thiocarbonyl ylides has attracted less attention. In order to study the chemoselectivity, a multifunctional molecule with different dipolarophilic moieties is necessary. The aim of the present study was to compare dipolarophilic reactivities of electron-rich and electron-poor C,C-double bonds in 1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (**2**)[21] towards **1a**-**c**. It was expected that the C=O groups in **2** would not be involved in the reactions with **1**. Whereas C=O groups of aromatic aldehydes and activated ketones intercept **1a**-**c**,[22,23] α,β-unsaturated carbonyl compounds were reported to undergo addition with the C=C bond to give tetrahydrothiophenes exclusively.[1,4]

The *endo*-dione (**2**) selected for our study is easily available by the *Diels-Alder* reaction of cyclopentadiene with 1,4-benzoquinone.[21] This compound is an important molecule for the preparation of 'cage compounds' as well as some natural products (triquinanes).[24] On the other hand, to the best of our knowledge, its use in 1,3-dipolar cycloadditions is limited to its reaction with benzonitrile oxides. In the case of *in situ* generated benzonitrile oxide, cycloadduct (**3**) was obtained (*Scheme 1*).[25]

Scheme 1



2

3

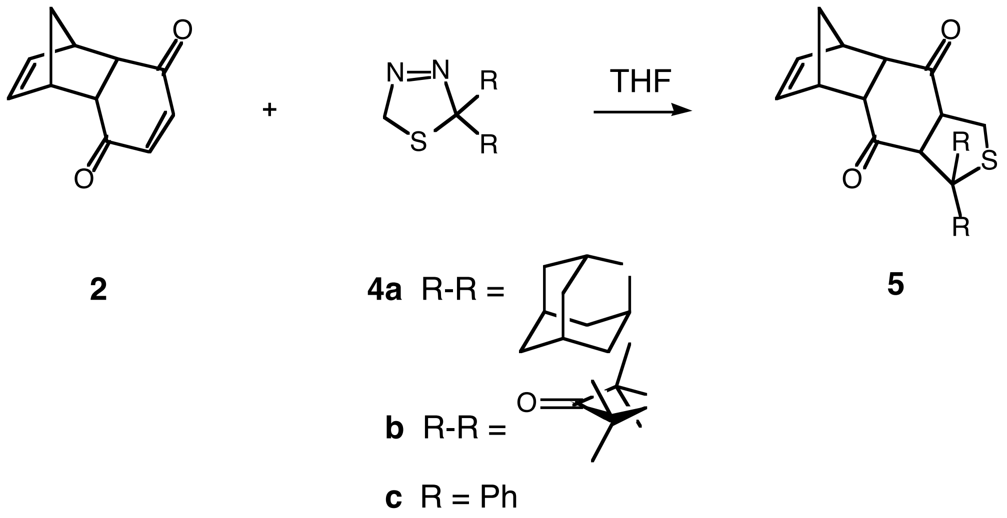
RESULTS AND DISCUSSION

Thiocarbonyl ylides (**1a**,**b**) were generated in THF solutions in the presence of **2** by thermal elimination of N_2 from the corresponding 2,5-dihydro-1,3,4-thiadiazoles at 45°C as reported for other reactions with these dipoles.[1,2] In the case of **1c**, its precursor, 2,5-dihydro-2,2-diphenyl-1,3,4-thiadiazole (**4c**), prepared at -70°C from thiobenzophenone and diazomethane, undergoes a cycloreversion with release of N_2 at -45°C.[26] The ^{1}H-NMR spectroscopic analysis of the crude product obtained after evaporation of the solvent revealed the complete conversion of **2**, and in each case, only a single product was detected.[27] Based on the spectroscopic data of the isolated products, it turned out that 1:1 cycloadducts had been formed in which the olefinic moiety incorporated in the norbornene skeleton was preserved. Therefore, we concluded that **2** is a reactive dipolarophile for thiocarbonyl ylides (**1**), and in the formation of cycloadducts, only the electron-deficient C=C bond is involved. For the obtained products, structures **5a**-**c** were proposed on the basis of the spectroscopic data (*Scheme 2*).

For example, product (**5a**) showed in the IR spectrum a strong absorption at 1700 cm^{-1} for non-conjugated C=O. In the ^{1}H-NMR spectrum, a characteristic resonance of two olefinic H-atoms appeared *ca.* 6.12 ppm (triplet-like). The C-atoms of this fragment absorbed in the ^{13}C-NMR spectrum at 137.4 and 135.8 ppm. In addition, singlets for 2 C=O at 209.8 and 208.7 ppm and a singlet for C(6) at 72.0 ppm are present along with 7 triplets for CH_2 and 10 doublets for CH. The EI-MS showed $M^{+\cdot}$ at m/z 354 as the base peak. All these data are in good agreement with structure (**5a**).

In order to establish further details of the structure of **5a**, especially the stereochemical relations, an X-Ray crystal-structure determination was carried out which confirmed the

Scheme 2



postulated structure (*Figure 1*). Furthermore, the orientation of the tetrahydrothiophene ring reveals that the 1,3-dipolar cycloaddition occurred from the *exo* side of **2**.

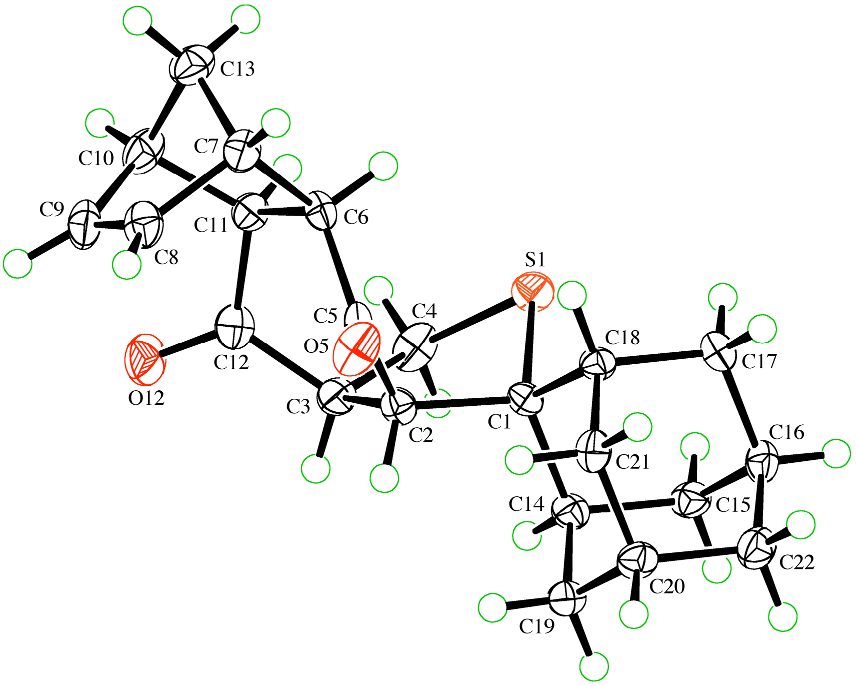


Figure 1. ORTEP plot[28] of the molecular structure of **5a** (arbitrary numbering of the atoms; 50% probability ellipsoids)

For cycloadducts (**5b**) and (**5c**), the comparison of the spectroscopic data showed the analogy of the structures with **5a**.

In summary, the presented results show that dione (**2**) is a prone dipolarophile and easily reacts with electron-rich thiocarbonyl ylides. The cycloadditions take place in a chemo- and stereoselective manner: the formation of the terahydrothiophene ring occurs exclusively at the electron-deficient site *via* the *exo*-approach of the dipole.

EXPERIMENTAL

General remarks. See ref.[29] IR spectra in KBr (cm^{-1}), NMR spectra at 200 (^{1}H) and 50.4 (^{13}C) in $CDCl_3$, EI-MS at 70 eV, and CI-MS with NH_3.

Starting materials. 1,4,4a,8a-Tetrahydro-1,4-methanonaphthalene-5,8-dione (**2**) was prepared from 1,4-benzoquinone and cyclopentadiene according to ref.[21] 2,5-Dihydro-1,3,4-thiadiazoles (**4a**) and (**4b**) were synthesized from the corresponding thioketones and diazomethane as described earlier.[30,31] The unstable 2,5-dihydro-2,2-diphenyl-1,3,4-thiadiazole (**4c**) was prepared *in situ* from thiobenzophenone and diazomethane at –60°C as reported by *Huisgen*.[32]

Reactions of 1a and 1b with 2. **General procedure**. A solution of dione (**2**) (170 mg, 1 mmol) and 1.1 mmol of the corresponding precursor (**4a**) and (**4b**) in dry THF (1 mL) was heated under magnetic stirring at 45°C (oil bath). The reaction flask was connected with a gas-burette and the volume of evolved nitrogen was controlled. After 5 h, the evolution of nitrogen was complete (*ca.* 25 mL), the solvent was evaporated and the solid residue was examined by ^{1}H-NMR spectroscopy. After crystallization from methanol, crude products (**5a**) and (**5b**), respectively, were filtered and recrystallized from methanol/dichloromethane affording analytically pure samples.

5'-Thiaspiro[adamantane-2,4'-tetracyclo[7.4.1^{10,13}.0^{3,7}]tetradec-11-ene]-2',8'-dione (**5a**). Yield: 210 mg (59%). Colorless needles ($MeOH/CH_2Cl_2$); mp 193-195°C. IR: 1700*vs* (2 C=O), 1450*m*, 1305*m*, 1250*m*, 1200*m*, 1155*m*, 790*w*, 730*m*. ^{1}H-NMR: 6.12 (*t*, *J* = 1.6, 2 H); 3.63 (*t*, *J* = 1.6, 2 H); 3.31-3.05 (*m*, 7 H); 2.60 (*d*, *J* = 12.7, 1 H); 2.28 (*d*, *J* = 13.2, 1 H); 2.12 (*s*, 1 H); 1.93-1.44 (*m*, 10 H); 1.43, 1.31 (2 *d*, *J* = 8.5, 2 H). ^{13}C-NMR: 209.8, 208.7 (2 C=O); 137.4, 135.8 (CH=CH); 72.0 (C_q); 62.2, 56.3, 55.9, 50.6 (4 CH); 47.1 (CH_2); 45.4, 44.2 (2 CH); 38.1, 37.8 (2 CH_2); 36.1, 35.2 (2 CH); 34.5, 34.0, 33.8, 33.2 (4 CH_2); 27.2, 26.9 (2 CH). EI-MS: 355 (45, $[M+1]^+$), 354 (100, $M^{+\cdot}$), 287 (21), 242 (24), 227 (49), 180 (99), 175 (60), 166 (74). Anal. Calcd for $C_{22}H_{26}O_2S$: C, 74.53; H, 7.39. Found: C, 74.99; H, 6.94.

2,2,4,4-Tetramethyl-5'-thiaspiro[cyclobutane-1,4'-tetracyclo[7.4.1^{10,13}.0^{3,7}]tetradec-11-ene]-2',3,-8'-trione (**5b**). Yield: 190 mg (55%). Colorless prisms (MeOH/CH_2Cl_2); mp 170-172°C. IR: 1780*vs* (C=O), 1695*vs* (2 C=O), 1470*m*, 1240*m*, 1190*m*, 1060*m*, 1040*m*. ^{1}H-NMR: 6.37, 6.20 (2*m*, 2 H); 3.60-2.74 (*m*, 8 H); 1.57, 1.47 (2 *m*, 2 H); 1.44 (*s*, Me); 1.27, 1.22 (2 *s*, 2 Me each). ^{13}C-NMR: 219.0 (C=O); 208.4, 206.9 (2 C=O); 137.7, 135.1 (CH=CH); 68.5, 64.8, 61.5 (3 C_q); 57.0, 56.8, 51.2, 50.7 (4 CH); 49.9 (CH_2); 49.7, 47.9 (2 CH); 31.6 (CH_2); 23.9, 22.7, 21.6, 20.6 (4 Me). EI-MS: 344 (9, $M^{+\cdot}$), 274 (100), 208 (99), 180 (25), 126 (40), 125 (46), 111 (87). Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02. Found: C, 69.89; H, 6.73).

Reaction of 1c with 2. A magnetically stirred solution of blue thiobenzophenone (198 mg, 1 mmol) in ether (2 mL) under an atmospere of N_2 was cooled to –70°C in an acetone/dry ice bath. An etheral solution of diazomethane was added until the blue color of the solution vanished. Subsequently, a solution of **2** (160 mg, 0.95 mmol) in dichloromethane (0.5 mL) was added and the temperature of the cooling bath was increased to –40°C. After 4 h, the cooling bath was removed and the reaction mixture was stirred for 1 h at rm. After this time, 115 mg of a colorless solid was filtered, the mother liquor was evaporated and the residue separated by column chromatography (SiO_2, petroleum ether with increasing amounts of dichloromethane). The most polar fraction isolated with petroleum ether/dichloromethane 7:3 was identical with the filtered solid. Therefore, both portions were combined (198 mg, 51%) and recrystallized from hexane/dichloromethane to afford analytically pure *4,4-diphenyl-5-thiatetracyclo[7.4.1^{10,13}.0^{3,7}]-tetradec-11-ene]-2,8-dione* (**5c**). Yield: 150 mg (39%). Colorless prisms; mp 168-170°C. ^{1}H-NMR: 7.59-6.90 (*m*, 10 H); 6.19, 5.98 (2 *m*, 2 H); 4.12-3.90 (*m*, 2 H); 3.36 (*s*, 1 H); 3.08-2.81 (*m*, 3 H); 2.20, 1.97 (2*m*, 2 H); 1.30, 1.00 (2 *d*, J = 8.5, 2 H). ^{13}C-NMR: 209.6, 207.6 (2 C=O); 146.0, 141.1 (2 arom. C_q); 137.3, 135.0 (CH=CH); 129.8, 128.4, 128.1, 128.0, 127.8, 127.7 (10 arom. CH); 63.2 (C_q); 55.1, 53.8, 49.8, 49.2 (4 CH); 49.1 (CH_2); 48.2 (2 CH); 30.5 (CH_2). CI-MS: 404 (87, $[M+NH_4]^+$), 387 (100, $[M+1]^+$), 350 (9), 338 (10), 321 (23), 199 (12). Anal. Calcd for $C_{25}H_{22}O_2S$: C, 77.69; H, 5.74. Found: C, 77.51; H, 5.42).

X-Ray Crystal Structure Determination of **5a** (see *Table 1* and *Figure 1*).[33] All measurements were made on a *Nonius KappaCCD* diffractometer[34] using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) and fitted with an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in *Table 1*, and a view of the molecule

Table 1. *Crystallographic Data of Compound* (**5a**)

Crystallised from	CH_2Cl_2 / MeOH
Empirical formula	$C_{22}H_{26}O_2S$
Formula weight [g mol^{-1}]	354.51
Crystal color, habit	colorless, plate
Crystal dimensions [mm]	0.08 × 0.20 × 0.25
Temperature [K]	160(1)
Crystal system	orthorhombic
Space group	$Pna2_1$
Z	4
Reflections for cell determination	2872
2θ range for cell determination [°]	4-60
Unit cell parameters a [Å]	23.6371(3)
b [Å]	11.4073(1)
c [Å]	6.3378(1)
V [Å^3]	1708.90(4)
D_x [g cm^{-3}]	1.378
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.203
$2\theta_{(\max)}$ [°]	60
Total reflections measured	39139
Symmetry independent reflections	4811
Reflections used [$I > 2\sigma(I)$]	3939
Parameters refined	227
Final R, wR	0.0400, 0.0319
Weights	$[\sigma^2(F_o) + (0.005F_o)^2]^{-1}$
Goodness of fit	1.431
Secondary extinction coefficient	1.5(2) × 10^{-6}
Final $\Delta_{\max}/\sigma$	0.0009
$\Delta\rho$ (max; min) [e Å$^{6-3}$]	0.46; -0.29

is shown in *Figure 1*. Data reduction was performed with *HKL Denzo* and *Scalepack*.[35] The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using SIR92,[36] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions [d(C–H) = 0.95 Å] and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. Refinement of the structure was carried out on F using full-matrix least-squares procedures, which minimised the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied. Two reflections, whose intensities were considered to be extreme outliners, were omitted from the final refinement. The space group symmetry dictates that the compound is racemic, but the space group contains a polar axis. Refinement of the absolute structure parameter[37] yielded a value of 0.55(5), which indicates that the crystals are merohedral twins. Neutral atom scattering factors for non-hydrogen atoms were taken from ref.[38a], and the scattering factors for H-atoms were taken from ref.[39] Anomalous dispersion effects were included in F_c;[40] the values for f' and f'' were those of ref.[38b] The values of the mass attenuation coefficients are those of ref.[38c] All calculations were performed using the *teXsan* crystallographic software package.[41]

ACKNOWLEDGMENTS

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