INVERSE [4+1] CYCLOADDITIONS OF 3-METHYL-2,3-DIHYDRO-1,3-BENZOTHIAZOLE-2-YLIDENE WITH 1,2,4,5-TETRAZINES

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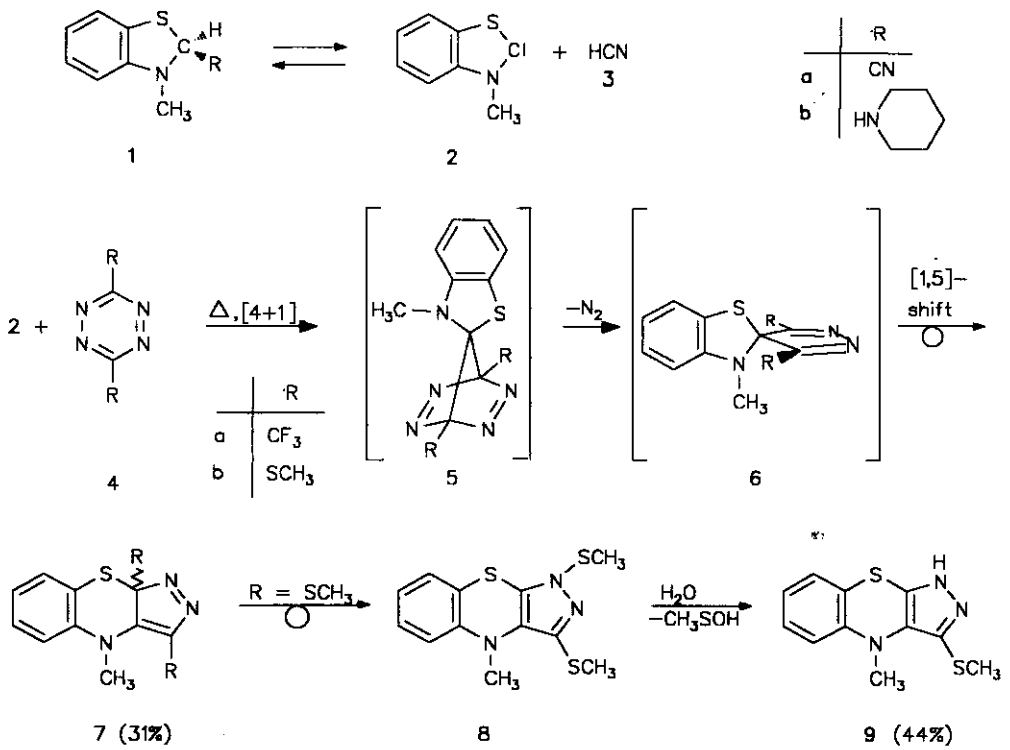
Abstract - [4+1] Cycloadditions of the nucleophilic singlet carbene 3-methyl-2,3-dihydro-1,3-benzothiazole-2-ylidene (**2**) with the electron-deficient s-cis-fixed diazadiene systems of a series of substituted 1,2,4,5-tetrazines (**4a-c**), with CF_3, SCH_3 and C_6H_5-groups are described together with some unexpected follow-up reactions.

In the course of our work[1-4] on cheletropic [4+1] cycloadditions of nucleophilic singlet carbenes[5-9] to cyclic diazadiene systems we have recently included 3-methyl-2,3-dihydro-1,3-benzothiazole-2-ylidene (**2**)[10-14] in our studies. The present paper reports successful transformations of this heterocyclic amino-thio-carbene with the differently substituted 1,2,4,5-tetrazines (**4a-c**).

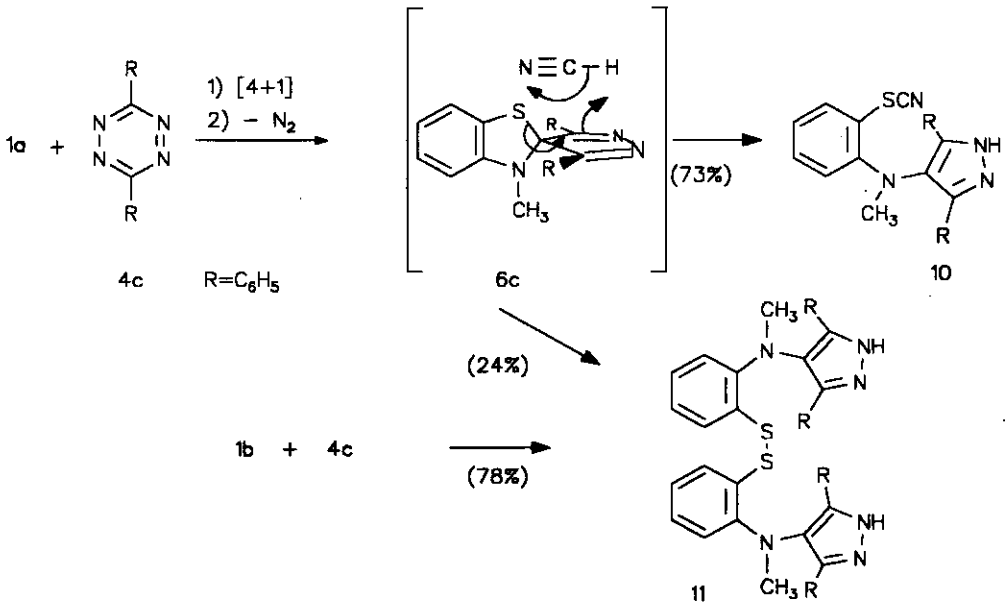
We used the cyano-substituted benzothiazoline (**1a**)[15] as a safe carbene source. **1a** is readily accessible from 3-methyl-benzothiazolium iodide and potassium cyanide, and easy to handle. On adding a satured solution of **1a** to **4a** in boiling benzene, decolourization of the red solution occurs rapidly. Work-up by column chromatography yields an orange substance whose analytical and spectroscopic data are in accord with constitution (**7a**). The formation of **7a** seems plausible if one assumes the [4+1] cycloadduct (**5a**) and the strained spiro compounds (**6a**) (formed by elimination of elemental nitrogen) to be non-isolable intermediates. **6a** finally stabilizes itself by a [1,5] sigmatropic rearrangement of the thiazole sulfur atom, giving **7a**. The reaction of **1** with **4b** is interpreted analogously to the stage of the tricyclic heterocycle (**7b**). After that, the pronounced tendency of the angular methylthio group to migrate occasions another sigmatropic shift , yielding the sulfenic acid amide (**8**) .

[1]Dedicated to Prof. E. C. Taylor on the occasion of his 70th birthday.



8, in turn, is probably hydrolyzed during chromatography on silica gel and transformed to the stable pyrazole derivative (**9b**), isolated as a beige solid in 44% yield. The reaction of **1a** with the phenyl-substituted tetrazine (**4c**) took a surprising turn. The main product was the phenyl thiocyanate (**10**), isolated as colourless crystals in 73% yield. In addition, small amounts of the disulfide (**11**) were isolated as a pale yellow crystalline powder. The structures of both compounds agree with their analytical and spectroscopic data.[16] The unusual formation of the phenyl thiocyanate (**10**) is explainable if one assumes **6c** to form intermediately. **6c** then reacts with the hydrogen cyanide liberated from **1a**. The cyanide ion presumably attacks the bivalent sulfur atom occasioning ring opening as indicated by the arrows, and subsequent protonation of the nitrogen atom of the pyrazole ring. The formation of the disulfide (**11**) is complex and cannot be explained without having isolated intermediate products. Interestingly, **11**

was the only product isolated (yield, 78%) from the reaction of **1b** with **4c**, taking no account of the piperidine eliminated from **1b**.



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EXPERIMENTAL PART

Hplc was done with a Merck-Hitachi Liquid Chromatograph. Melting points are uncorrected. Ir spectra were recorded with Perkin-Elmer spectrophotometers 257 and 398, nmr spectra with Varian T60 and XL100 and Jeol JNM-FX100 and -GX400, mass spectra with Vacuum Generators 7070 (70 eV) spectrometers.

4-Methyl-3,9a-bis(trifluoromethyl)-9a*H*-pyrazolo[3,4-*b*][1,4]benzothiazine (7): A solution of **4a** (0.65 g, 3 mmol) in 10 ml of dry benzene is heated to reflux while a saturated solution of **1a** (0.53 g, 3 mmol) is added until the red colour of the tetrazine is faded (after about two thirds of the stoichiometric amount). The solvent is evaporated in vacuo, and the residue was chromatographed on silica gel (column, 30 x 3 cm; eluent: n-hexane/ethyl

acetate 8+2). **7** is eluted as an orange-yellow fraction and crystallized from n-hexane, yielding 0.24 g (31%, related to **1**), mp 113°C. Ir (KBr): ν = 3105 cm^{-1}, 1600, 1580, 1570, 1480, 1440, 1425, 1400, 1215, 1195, 1175, 1125, 1110, 760. Uv (CH_2Cl_2): λ_{max} (lg ε) = 261 nm (3.701), 280 (3.783), 285 (3.832), 341 (3.581), 416 (3.809). ^{1}H-Nmr (400 MHz, $CDCl_3$): δ = 7.46-7.23 (4 H, m, phenyl H), 3.73 (3 H, q, CH_3, J_{HF}= 2.0 Hz). ^{13}C-Nmr ($CDCl_3$): δ = 147.3 (s, broad, C-3a, J_{CF} = 1 Hz), 137.9 (dd; C-4a, $^3J_{CH}$ = 7/5 Hz), 128.0/127.9 (2d; 2 phenyl CH, $^1J_{CH}$ = 168/170 Hz), 127.4 (q, C-3, $^2J_{CF}$ = 38 Hz), 126.2 (d, phenyl CH, $^1J_{CH}$ = 172 Hz), 122.1 (q, CF_3, $^1J_{CF}$ = 287 Hz), 121.5 (q, CF_3, $^1J_{CF}$ = 269 Hz), 116.1 (d, C-5, $^1J_{CH}$ = 160 Hz), 111.4 (dd, C-8a, $^3J_{CH}$ = 10/7 Hz), 83.8 (q, C-9a, $^2J_{CF}$ = 30 Hz), 40.0 (qq, CH_3, $^1J_{CH}$ = 142 Hz, J_{CF} = 4 Hz). Ms (70 eV, 30°C): m/z (%) = 339 (100) [M$^+$], 341 (14). Anal. Calcd for $C_{12}H_7N_3F_6S$: C, 42.48 ; H, 2.08; N, 12.39. Found: C, 42.74; H, 2.11; N, 12.40.

4-Methyl-3-methylthio-1*H*-pyrazolo[4,5-*b*][1,4]benzothiazine (9): A solution of **1b** (0.47 g, 2 mmol) and **4b** (0.70 g, 2 mmol) in 5 ml of dry benzene is heated to reflux under nitrogen for 30 min. The solvent is removed in vacuo, and the residue was chromatographed on silica gel (column, 40 x 3 cm). n-Hexane/dichloromethane (1+1) elutes **1b**, ethyl acetate impure **9**, which after a second chromatographic purification (column, 30 x 3 cm; eluent: n-hexane/ethyl acetate 6 +4) is isolated as a yellow oil that solidifies on drying in a vacuum. After several washings with a mixture of n-pentane and ether (9 +1) a beige solid is obtained. Yield, 0.22 g (44%), mp 49-52°C. Ir (KBr): ν = 3140 cm^{-1}, 2960, 1555, 1475, 1410, 1310, 1285, 755. ^{1}H-Nmr (400 MHz, DMSO-d_6): δ = 12.81 (s, broad, 1 H, NH), 7.12 (1H, m), 7.04 (1H, m), 6.85-6.79 (2H, m, 4 phenyl H), 3.43 (3 H, s, NCH_3), 2.38 (3 H, s, SCH_3). ^{13}C-Nmr ($CDCl_3$): δ = 144.7 (s, C-4a), 135.3 (s*) / 129.9 (s, 2 phenyl C), 127.8/127.4 (2d, C-6/8, $^1J_{CH}$ = 160 Hz each), 121.2 (d, C-7, $^1J_{CH}$ = 162 Hz), 120.1 (s, C-8a), 118.8 (s*, phenyl C), 113.6 (d, C-5, $^1J_{CH}$ = 158 Hz), 35.4 (q, NCH_3, $^1J_{CH}$ = 138 Hz), 21.6 (q, SCH_3, $^1J_{CH}$ = 141 Hz). *Signals show marked line broadening due to tautomeric equilibrium of the pyrazole system. Ms(70 eV, 130°C): m/z (%) =249 (100) [M$^+$], 234 (54) [M$^+$-CH_3]. Anal. Calcd for $C_{11}H_{11}N_3S_3$: C, 52.99; H, 4.45; N, 16.85; S, 25.72. Found: C, 52.96 H, 4.50; N, 16.44; S, 26.00.

Reaction of **1a** *and* **4c**: A solution of **4c** (0.47 g, 2 mmol) in 6 ml of dry toluene is heated to reflux under nitrogen. **1a** (0.35 g, 2 mmol), dissolved in toluene (10 ml), is added dropwisely. After refluxing for 1 h, the solvent is evaporated and the residue was chromatographed on silica gel (column, 30 x 3 cm). With dichloromethane

unreacted tetrazine was eluted. A mixture of n-hexane and ethyl acetate (1:1) eluted the phenyl isothiocyanate (**10**) (pale yellow solid), pure ethyl acetate the disulfide (**11**) (pale yellow powder).

Methyl(3,5-diphenyl-1*H*-pyrazol-4-yl)-(2-thiocyanatophenyl)amine (10): Yield 0.53 g (73%), colourless crystals, mp 182°C (acetone). Ir (KBr): ν = 3310 cm^{-1} (NH), 2165 (SCN), 1585, 1480, 1455, 1445, 960. Uv (CH_2Cl_2): λ max (lg ε) = 231 nm (4.471), 281 (sh, 4.012). ^{1}H-Nmr (400 MHz, DMSO-d_6): δ = 13.42 (1 H, s, broad, NH), 7.77 (2H, s, broad, phenyl H), 7.49 (2H, s, broad, phenyl H), 7.36-7.07 (9H, m, phenyl H), 6,74 (1H, m, 4'-H), 3.22 (3 H, s, CH_3). ^{13}C-Nmr * (DMSO-d_6): δ = 147.9, 146.0, 137.6, 132.5, 131.3, 129.6, 128.3, 127.7, 126.4, 124.2, 120.7, 117.6, 111.9, 111.2, 41.7. Ms (70 eV, 60°C): m/z (%) = 382 (13) [M^+], 355 (33), 354 (29), 252 (68), 149 (100). *The phenyl substituents are recorded isochronically because of the tautomeric equilibrium of the pyrazole system. Anal. Calcd for $C_{23}H_{18}N_4S$: C, 72.23; H,4.74; N, 14.65; S, 8.38. Found: C, 71.96; H, 4.83; N, 14.44; S, 8.04.

Bis{2-[(3,5-Diphenyl-1*H*-pyrazol-4-yl)methylamino]}diphenyl disulfide (11): Yield 174 mg (24%) pale yellow crystals, mp 257°C [decomp. n-hexane/ethyl acetate 1+1]. Ir (KBr): ν = 3390 cm^{-1} (broad, NH), 3190, 1585, 1470, 1450, 1330, 1270, 755. ^{1}H-Nmr (400 MHz, DMSO-d_6)* : δ = 13.18 (1H, s, broad, NH), 7.80 (2H, s, broad, phenyl H), 7.46 (2H, s, broad, phenyl H), 7.30-7.20 (6H, m, phenyl H), 6.99 (1H, m, 4'-H), 6.89 (1H, m, 3'-H), 6.63 (1H, m, 6'-H), 6.47 (1H, m, 5'-H), 3.14 (3 H, s, CH_3). *Relative integrals; multiply by two to get absolute number of protons. ^{13}C-Nmr (DMSO-d_6): δ = 146.5, 146.2, 137.7, 133.0, 128.2, 127.4, 126.7, 126.5, 126.0, 125.5, 123.3,119.6, 116.2, 41.8. The phenyl substituents are recorded isochronically because of the tautomeric equilibrium of the pyrazole system, but show considerable line broadening. Ms (70 eV, 250°C): m/z (%) = 357 (100) [1/2 M^+ + H]. Anal. Calcd for $C_{44}H_{36}N_6S_2$: C, 74.13; H, 5.09; N, 11.79; S, 9.00. Found: C, 73.50; H, 5.05; N, 11.63; S, 9.04.

Reaction of 3-methyl-2-piperidinobenzothiazoline (1b) with 4c: A solution of **1b** (0.56 g, 2.4 mmol) and **4c** (0.47 g, 2.0 in 10 ml of dry xylene is heated to reflux for 1 h. The residue after removal of the solvent in vacuo is separated chromatographically on silica gel (column, 40 x 3 cm). The fractions eluted with dichloromethane contain residual xylene, **4c**, and piperidine and are discarded. Ethyl acetate elutes **11** that is purified by crystallization as described above. Yield, 556 mg (78%).

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