Intermolecular 1,3-Dipolar Cycloaddition of Benzonitrile Oxide to 2*H*-1,3-Benzothiazines and Hexahydro-4*H*-1,3-benzothiazine [1]

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Received September 7, 1990

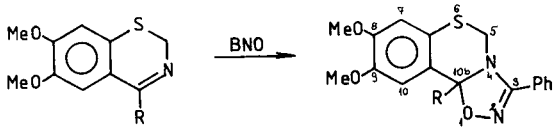
The thermal [3 + 2] intermolecular cycloaddition of benzonitrile oxide to 2*H*-1,3-benzothiazines **1a-g** and hexahydro-4*H*-1,3-benzothiazine (**5**) gives new types of tricyclic angularly and linearly condensed 1,2,4-oxadiazolo-1,3-benzothiazine-fused nitrogen-bridgehead ring systems **2a-g**, **6**.

J. Heterocyclic Chem., **28**, 481 (1991).

1,3-Dipolar cycloaddition is one of the most useful methods for the preparation of five-membered heterocycles. Numerous possibilities for variation are available by changing the structures of both the dipoles and the dipolarophiles. One of the most widely used reagents is benzonitrile oxide (BNO), a thoroughly investigated 1,3-dipolarophile.

Following our studies of the cycloaddition reactions of 1,3-benzothiazines [2-8], in this paper we report the reactions of 6,7-dimethoxy-2*H*-1,3-benzothiazine (**1a**) and its 4-substituted derivatives **1b-g** [9] with benzhydroximic chloride [10] in the presence of triethylamine, yielding the new angularly-condensed 1,2,4-oxadiazolo[4,5-*c*][1,3]benzothiazines **2a-g** (Scheme 1).

Schéma 1

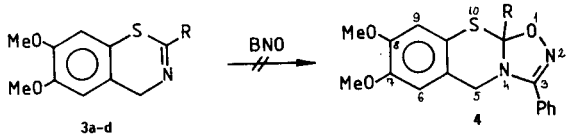


1a-g **2a-g**

a: R = H; **b**: R = Me; **c**: R = Et; **d**: R = CH_2Ph;
e: R = Ph; **f**; R = 4-ClC_6H_4;
g: R = 3,4-$(MeO)_2C_6H_3$

The attempted cycloaddition reactions of the isomeric 2-substituted 4*H*-1,3-benzothiazine derivatives **3a-d** with BNO under similar conditions, in the hope of obtaining the linearly-condensed 1,2,4-oxadiazolo[5,4-*b*][1,3]benzothiazine derivatives **4**, proved unsuccessful (Scheme 2).

Scheme 2

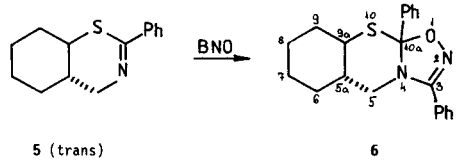


3a-d **4**

a: R = Me; **b**: R = CH_2Ph; **c**: R = Ph; **d**: R = 4-ClC_6H_4

We assume that the unsuccessful cycloaddition reactions of the 2-substituted 4*H*-1,3-benzothiazines **3a-d** can be attributed to electronic reasons. *trans*-2-Phenyl-4a,5,6,-7,8,8a-hexahydro-4*H*-1,3-benzothiazine (**5**) [11], which has considerably more basic properties than the 2-substituted 4*H*-1,3-benzothiazines **3**, reacted with BNO to furnish the isomeric linearly-condensed *trans*-3,10a-diphenyl-5*H*-1,2,4-oxadiazole[5,4-*b*][1,3]-5a,6,7,8,9,9a-hexahydrobenzothiazine (**6**) (Scheme 3). This seems to support our assumption.

Scheme 3



5 (trans) 6

The structures of the new compounds were confirmed by ^1H and ^{13}C nmr spectroscopy.

Structure Elucidation.

The ^1H and ^{13}C nmr data on compounds **2a-g** are given in Tables 1 and 2, and those on **6** in the Experimental. They prove the supposed structures unambiguously and are self-explanatory. It is to be noted that the benzne ring in position 10b causes an anisotropic shielding [12a] on the H-10 atoms in **2e-g** (*cf.* the upfield shifts of the H-10 singlets). This indicates the *cis* annelation of the two hetero rings. In the case of *trans* annelation, the *α-axial* benzene ring does not lie near enough to the H-10 atom for such an anisotropic interaction. Similarly, an upfield shift of the C-10 line in the ^{13}C nmr spectra was observed for compounds **2b-g** relative to **2a**, due to steric hindrance between the molecular skeleton and the 10b substituent (steric compression shift [13]).

Table 1

^{1}H NMR Chemical Shifts (δ_{TMS} = 0 ppm) and Characteristic Coupling Constants (Hz)

for Compounds **2a-g** in Deuteriochloroform Solution at 250.15 MHz

Compound	OCH_3 (8,9)		CH_2 (5) [a]		H-7	H-10	ArH^{m,p}	ArH^o	Signal of hydrogens in substituent R (10b)
	2 x *s*	(2 x 3H)	2 x *d*	(2 x 1H)	*s* (1H)	*s* (1H)	*m* (3H) [b]	*dd* (2H) [b]	
2a	3.86	3.90	4.46	4.53	6.71	6.89	~7.5	~7.7	H-10b, 6.62 s (1H)
2b	3.82	3.89	4.50	4.72	6.50	7.02	~7.65	~7.8	CH_3, 2.01 s (3H)
2c	3.84	3.90	4.52	4.70	6.52	7.00	~7.5	7.62	CH_3, 1.13 t (3H), J, 7.3, CH_2, 2.20, 2.35 2 x m (2 x 1H) [c]
2d	3.85	3.86	4.26	4.38	6.56	6.99	~7.5	7.61	CH_2, 3.50. 3.56 [a]
2e	3.82	3.64	4.46	4.65	6.58	6.68	~7.4 [d]	~7.6 [e]	ArH^o, ~7.6 [e], ArH^{m,p}, ~7.4 [d]
2f	3.71	3.86	4.48	4.64	6.60	6.64	~7.4 [d]	~7.55 [e]	ArH-3'-5', ~7.4 [d], ArH-2'6', ~7.55 [e]
2g	3.75	3.87	4.49	4.68	6.75	6.56	~7.5	7.61	OCH_3 (10b-Ar), 3.91 s (6H), ArH-5', 6.83 d (8.4), ArH-6', 6.92 dd, ArH-2', 7.31 d (2.0)

[a] *AB*-type spectrum, *J*, 13.8±0.3. [b] 3-Phenyl group. [c] *AB*part of an ABX_3 spectrum. [d,e] Overlapping multiplets.

Table 2

^{13}C NMR Chemical Shifts (δ_{TMS} = 0 ppm) of Compounds **2a-g** in Deuteriochloroform Solution at 20.14 MHz [a]

Compound	C-3	C-5	C-6,10,1'			C-7,10		C-8,9		OCH_3 (8,9)		C-2',6'	C-3',5'	C-4'
2a	157.6	48.3	120.9	125.5	126.7	112.6	113.7	148.1	149.9	56.2	56.3	129.3	128.3	131.0
2b	156.9	44.6	123.3	125.6	126.0	111.0	111.5	148.1	149.7	56.1	56.3	129.0	128.3	130.7
2c	156.3	44.0	123.1	125.1	125.4	110.7	111.2	147.5	149.2	55.6	55.9	127.8	128.5	130.2
2d	156.2	44.8	123.5	125.3	125.6	111.2	112.1	147.9	149.6	56.0	56.3	128.9 [b]	128.2 [b]	130.7
2e	156.0	43.9	123.4	124.8	125.0	110.3 [d]	113.2	147.3	149.6	55.8 [c]		128.1 [b]	128.7 [b,c]	130.6
2f	156.1	44.2	123.1	124.9	125.1	110.8 [d]	113.4	147.6	149.9	55.9	56.0	128.9 [b,c]	128.2 [b]	130.8
2g	155.7	43.2	123.2	124.4	124.8	110.0 [b,d]	113.7	147.1 [e]	149.6 [e]	55.6	55.7	128.5	127.8	130.3

Further signals: C-10b (**2a**): 92.9; CH_3 (**10b**): 27.7 (**2b**): CH_3(Et): 6.8 (**2c**); CH_2(Et): 31.7 (**2c**); CH_2(benzyl): 46.2 (**2d**); OCH_3(veratryl): 55.6, 55.7 (**2g**); C_{Ar}-signals (pos. 10b), C-1': 135.0 (**2d**), 142.0 (**2e**), 141.0 (**2e**), 141.0 (**2f**), 134.1 (**2g**); C-2',3',5',6': 128.0 [b], 130.2 [b] (**2d**), 127.5 [b], 128.0 [b] (2e), 128.9 [b,c], 128.3 [b] (**2f**); C-2',5' (**2g**): 110.5 [b], 110.7 [b]; C-3',4' (**2g**): 148.7 [e], 149.4 [e]; C-6' (**2g**): 130.3; C-4': 126.9 (**2d**), 128.7 [b,c] (**2e**), 134.9 (**2f**). [a] The measuring frequency was 62.89 MHz for compounds **2a** and **2g**. [b,e] Assignments interchangeable. [c] Two overlapping lines. [d] C-10.

Table 3

Physical and Analytical Data on Compound **2a-g** and **6**

Compound	Yield (%)	Mp (°C)	Molecular formula	MW	Analysis (Calculated/Found) C(%)	H(%)	N(%)
2a	67	199-200 [a]	$C_{17}H_{16}N_2O_3S$	328.39	62.17	4.91	8.53
					62.51	5.20	8.70
2b	53	178-179 [a]	$C_{18}H_{18}N_2O_3S$	342.41	63.14	5.30	8.18
					63.25	5.50	8.30
2c	63	163-164 [b]	$C_{19}H_{20}N_2O_3S$	356.44	64.02	5.66	7.86
					64.30	5.85	7.96
2d	32	138-139 [c]	$C_{24}H_{22}N_2O_3S$	418.51	68.78	5.30	6.70
					70.00	5.52	6.95
2e	65	133-134 [d]	$C_{23}H_{20}N_2O_3S$	404.48	68.29	4.98	6.93
					68.52	5.24	6.95
2f	66	153-154 [b]	$C_{23}H_{19}ClN_2O_3S$	438.92	62.93	4.36	6.38
					62.79	4.42	6.35
2g	62	153-154 [b]	$C_{25}H_{24}N_2O_5S$	464.53	64.64	5.21	6.03
					64.38	5.32	6.22
6	55	125-130 [e]	$C_{21}H_{22}N_2OS$	350.48	71.96	6.33	8.00
					71.76	6.50	8.26

Solvent: [a] benzene, [b] ethanol, [c] diethyl ether, [d] methanol, [e] tetrachloromethane.

The unaltered *trans* annelation of the cyclohexane and thiazine rings in compound **6** follows from the couplings of 5ax, 5a and 9ax, 9a, which have magnitudes (11.6 and 11.0 Hz) typical of *diaxial* interactions [12b]. The configuration of C-10a (the steric position of the phenyl substituent on this carbon) can be determined by starting from the observation that one of the hydrogens in positions 5a, 6, 7, 8, 9 is extremely shielded in compound **6** (the chemical shift being 0.65 ppm).

Such a shielding is expected only for the steric structure involving the 10a *R** configuration (with the 10a-phenyl ring *cis* to H-5a and *trans* to H-9a) and *cis* annelated hetero rings. In this structure (Figure 1), H-5a is strongly shielded by the close-lying 10a phenyl ring. This supposed structure is also supported by the observations discussed in points i-iii.

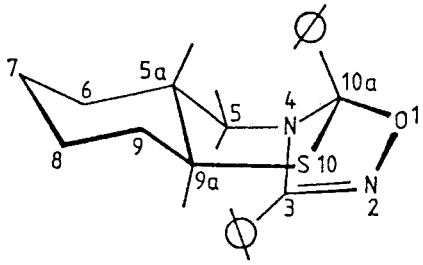


Figure 1

i. In the case of *trans* annelation, anisotropic shielding would be expected for H-9a, which is in the 1,3-*diaxial* position with the 10a phenyl ring in this structure. However, the upfield shift of the signal of this hydrogen is of practically the same magnitude (0.64 ppm) as for the 5-methylene atoms (0.54 and 0.59 ppm) relative to those measured for the starting cyclophile **5** [14] and can be attributed to the saturation of the C=N double bond.

ii. The structure with *trans* annelated hetero rings has a strained skeleton and is therefore sterically unfavorable.

iii. In the structure having *cis* annelated hetero rings and the 10a *S** configuration, a similar upfield shift of the H-9a signal would be expected to that mentioned in point i, while the observed shielding of H-5a is not explainable for this steric structure.

EXPERIMENTAL

Melting points are uncorrected.

The ^{1}H nmr spectra were recorded in deuteriochloroform solution in 5 mm tubes at room temperature, on a Bruker WM-250 FT spectrometer controlled by an Aspect 2000 computer at 250.13 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: sweep width 5 kHz, pulse width 1 μs (~20° flip angle), acquisition time 1.64 s, number of scans 16, computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line width 0.7 Hz) was applied.

The ^{13}C nmr spectra were recorded in deuteriochloroform solution in 5 or 10 mm tubes at room temperature on a Bruker WM-250 or WP-80SY FT spectrometer controlled by an Aspect 2000 computer at 62.89 or 20.15 MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important acquisition and data processing parameters for the ^{13}C nmr spectra were as follows: sweep width 15 and 5 kHz, pulse width 7.5 and 3.5 μs (~30° flip angle), memory size 32 and 16 K, acquisition time 0.5 and 1.64 s, number of scans 0.5-3 K, complete proton noise decoupling with ~1 and ~3 W power, Lorentzian exponential multiplication of line width 2.0 and 1.0 Hz for signal-to-noise enhancement, repetition rate 2 s.

DEPT [15] spectra were run in a standard way [16], using only the θ = 135° pulse to separate CH/CH$_3$ and CH$_2$ lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-512, relaxation delay for protons 3 s, 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

General Procedure for the Preparation of Compounds **2a-g** and **6**.

Compounds **1a-g** or **5** (3.3 mmoles) was dissolved in benzene (20 ml) and 3.3 mmoles of benzhydroximic chloride was added. A solution of triethylamine (3.3 mmoles) in 10 ml of benzene was added dropwise to the mixture, with stirring, during 1 hours. The benzene solution was extracted with diluted hydrochloric acid, dried (sodium sulfate) and evaporated, and the residue was then crystallized (*cf.* Table 3).

Compound **6**.

This compound had ^{1}H nmr (deuteriochloroform): 250 MHz, δ ppm H-5a, 0.65 m (1H), CH$_2$(6-9), 1.1-1.5 and 1.6-1.8 2 x m (5 + 3H), H-9a; 2.46 dt (J, 11.0, 11.0, 3.5 Hz), H-5, 2.76 dd (J, 14.8, 11.6 Hz) and 3.46 dd (J, 14.8, 3.7 Hz), ArH; 7.4-7.6 m (6H), ArH^{ortho}-(10b-Ph), ~7.65 m (2H), ArH^{ortho}(3-Ph); 8.05 m (2H); ^{13}C nmr (deuteriochloroform): 62.89 MHz, δ ppm CH$_2$ (7,8), 25.4, 25.7, CH$_2$ (6), 29.1, CH$_2$ (9), 32.3, CH (5a), 41.4, CH (9a), 45.1, CH$_2$ (5), 48.9, C-10a, 110.4, ArC-1(3-Ph), 124.7, ArC-2,6 and -3,5, 128.4, 128.5, 128.8, 128.9, ArC-4, 129.8, 130.6, ArC-1 (10a-Ph), 137.0, C-3, 158.5. Assignments were supported by DEPT measurements.

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