

Synthesis of 3,3'-Biisoxazoles from Cyanogen  
*N,N'*-Dioxide and Trimethylsilyl Enol Ethers *via*  
 the Corresponding 5,5'-Bis(trimethylsilyloxy)-3,3'- $\Delta^2$ -biisoxazolines

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Regioselective 1,3-dipolar cycloaddition of Cyanogen *N,N'*-dioxide (**2**) to trimethylsilyl enol ethers **3a-d**, **6** and **7** gave the corresponding 5,5'-bis(trimethylsilyloxy)-3,3'- $\Delta^2$ -biisoxazolines which upon short heating with 10% hydrochloric acid afforded 3,3'-biisoxazoles **5a-d**, **8** and **9**. Only the intermediate 5,5'-bis(trimethylsilyloxy)-derivative **4a** was isolated and studied. Reaction of **2** with vinyl methyl ketone (**10**) gave biisoxazoline **11** which by oxidation with  $\gamma$ -manganese dioxide gave biisoxazole **12**.

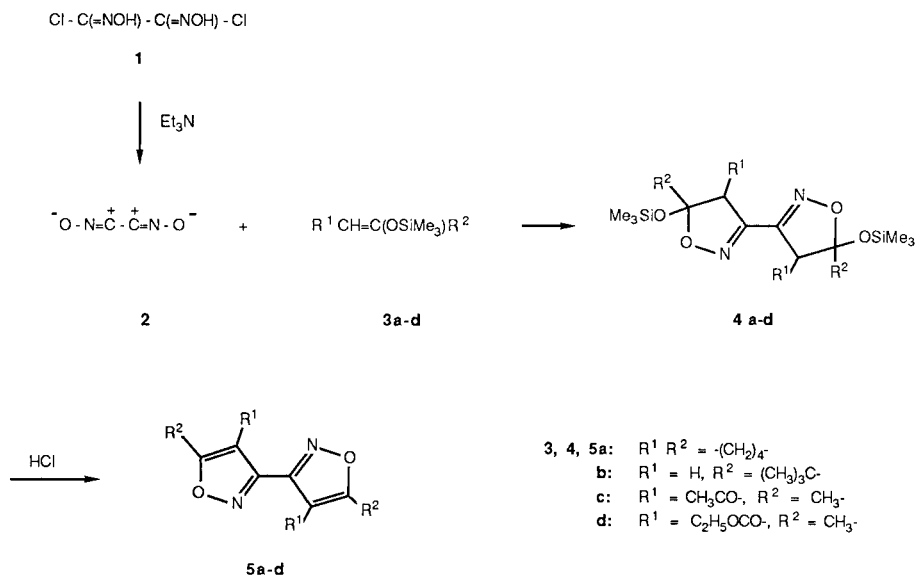
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3,3'-Biisoxazoles have been prepared by various types of ring closure, similar to those reported for the synthesis of isoxazoles [1,2]. Of special interest are methods for direct synthesis of 3,3'-biisoxazoles as the reaction of acetylenic Grignard reagents with dichloroglyoxime (**1**) [1,3] and the reaction of Cyanogen *N,N'*-dioxide (**2**) with acetylenes [2,4,5]. The utility of both these one-step synthetic methods is limited by the availability of the appropriate triple bond compounds. We reported previously regioselective reactions of simple nitrile *N*-oxides with some trimethylsilyl enol ethers to the corresponding 5-trimethylsilyloxy- $\Delta^2$ -isoxazolines and their subsequent transformation to isoxazoles, *via* 1,2-elimination of the trimethylsilyloxy group and of the C<sub>4</sub>-hydrogen atom [6]. Recently some similar reactions have been reported by Hosomi and his co-workers [7]. In connection with this work we report now

the synthesis of some 3,3'-biisoxazoles from bis-nitrile oxide **2** and the appropriate trimethylsilyl enol ethers, *via* the corresponding 5,5'-bis(trimethylsilyloxy)-3,3'- $\Delta^2$ -biisoxazolines. The synthesis of biisoxazoline **11** and its oxidation to biisoxazole **12** is also reported.

Trimethylsilyl enol ethers were prepared by silylation of the appropriate carbonyl compounds with chlorotrimethylsilane and triethylamine [8-10]. Compounds **3c** and **3d** were used as stereoisomeric mixtures (*cis:trans* 25:75 and 75:25 respectively). Compounds **6** (*cis:trans* 27:73) and **7** were obtained as a mixture (**6:7** = 88:12) by the silylation of butanone and were used in the reaction with compound **2** without separation. In all reactions studied the cyanogen *N,N'*-dioxide (**2**) was prepared *in situ* from dichloroglyoxime (**1**), by dropwise addition of triethylamine in dry ether. The reactions between **2** and dipolarophiles **3a-d** are depicted in Scheme 1.

Scheme 1



Treatment of two equivalents of compound **3a** with compound **2**, prepared *in situ* from one equivalent of **1** and separation of the reaction mixture by column chromatography afforded 5,5'-bis(trimethylsilyloxy)-3,3'-biisoxazoline **4a** in 15% yield. By heating a methanolic solution of compound **4a** with 10% hydrochloric acid for 10 minutes biisoxazole **5a** in 95% yield was obtained. Similarly, the reactions of **2** with compounds **3b-d** resulted to the formation of the corresponding biisoxazolines **4b-d** as it was established by their further transformation to the corresponding biisoxazoles **5b-d**. All efforts for the isolation of trimethylsilyloxy derivatives **4b-d** by chromatographic methods (column, ptlc) were unsuccessful. The difficulties in the separation of compounds **4** are due to the formation of biisoxazolines in diastereoisomeric forms, by analogy to similar products observed in the reported reactions of **2** with olefinic compounds [5]. Column chromatography for isolation of compound **4d** gave only biisoxazole **5d**. A gradual transformation into biisoxazole **5c** was also noticed in the attempted isolation of compound **4c** by column chromatography. A similar decomposition was also observed in the previously prepared 5-trimethylsilyloxy- $\Delta^2$ -isoxazolines [6]. The low yields for compounds **4** and **5** may be attributed to the expected polymerization of **2** to polyfuroxans and to the possible formation of bis-isoxazolylfuroxans [5].

Treatment of a mixture of compounds **6** (88%) and **7** (12%) with **2**, followed by heating of the reaction mixture with 10% hydrochloric acid in methanol, afforded 3,3'-biisoxazoles **8** and **9** (Scheme 2).

Although the lability of the isoxazole ring precludes the use of drastic conventional reagents for aromatizing dihydroisoxazoles, two satisfactory methods are now available for this transformation, bromination by *N*-bromosuccini-

imide [11] and oxidation with  $\gamma$ -manganese dioxide [12]. In an effort to investigate the preparation of 3,3'-biisoxazoles by oxidation of 3,3'- $\Delta^2$ -biisoxazolines we prepared compound **11** in 25% yield from **2** and vinyl methyl ketone (**10**) (Scheme 3). Oxidation of compound **11** with  $\gamma$ -manganese dioxide gave the expected 3,3'-biisoxazole **12**, in 32% yield.

The structure of all compounds prepared was confirmed by their analytical and spectral data, listed in Tables I, II. In agreement to the proposed structure the  $^1\text{H}$  nmr spectra of compounds **5b**, **9** and **12** displayed one singlet at  $\delta$  6.43 (4-H, 4'-H), 6.48 (4'-H) and 7.43 (4-H, 4'-H) respectively. The mass spectra of all compounds gave correct molecular ion, while the spectra of 3,3'-biisoxazoles **5b**, **5c**, **5d**, **8** and **9** gave the expected fragments  $\text{M} - \text{R}$ , ( $\text{R} = 5$  and/or 5'-alkyl substituent),  $\text{M} - \text{R}-\text{C}=\text{O}$  and  $\text{R}-\text{C}\equiv\text{O}$ , by analogy to the reported fragmentation pattern of 5-alkyl-substituted isoxazoles [13,14].

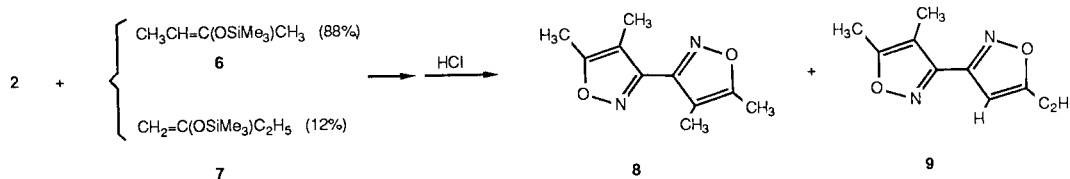
Although no efforts were made to optimize yields, the observed higher yield (45%) in the preparation of compound **5b** from equimolar amounts of **2** and **3b** indicates that the yields in the other reactions studied may be increased by using excess of compound **2**.

In conclusion the reported reactions offer an easy route for the preparation of 4,4'- and/or 5,5'-substituted 3,3'-biisoxazoles through regioselective 1,3-dipolar cycloaddition of bis-nitrile oxide **2** to the appropriate trimethylsilyl enol ethers, readily obtained by silylation of available carbonyl compounds.

## EXPERIMENTAL

Melting points were determined with a Kofler Hot-stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 297 spectrophotometer as Nujol mulls. The  $^1\text{H}$ -nmr spectra were recorded

Scheme 2



Scheme 3

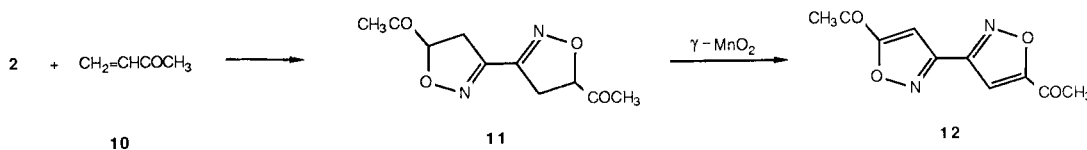


Table I  
Physical and Analytical Data of Compounds **4a**, **5a-d**, **8**, **9**, **11** and **12**

Compound	Yield %	Mp °C	Solvents [a] of Crystallization	Composition	Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
<b>4a</b>	15 [b,c]	105-107	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>20</sub> H <sub>36</sub> N <sub>2</sub> O <sub>4</sub> Si <sub>2</sub>	56.56	56.73	8.54	8.58	6.60	6.32
<b>5a</b>	95 [d]	189-191	CH <sub>2</sub> Cl <sub>2</sub> /PE	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	68.83	68.93	6.60	6.57	11.47	11.38
<b>5b</b>	45 [c,e]	128-130	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	67.71	67.66	8.12	8.12	11.28	11.15
<b>5c</b>	10 [b,c]	124-126	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	58.06	57.90	4.87	4.74	11.29	11.07
<b>5d</b>	3 [b,c]	oil	—	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>6</sub>	54.54	54.16	5.23	5.52	9.09	9.38
<b>8</b>	17 [b,f]	93-94	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	62.48	62.35	6.29	6.09	14.58	14.40
<b>9</b>	9 [b,f]	82-83	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	62.48	62.30	6.29	6.15	14.58	14.45
<b>11</b>	25 [b,c]	143-145	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O/PE	C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	53.57	53.30	5.39	5.24	12.50	12.72
<b>12</b>	32 [g]	185-187	CH <sub>2</sub> Cl <sub>2</sub> /PE	C <sub>10</sub> H <sub>8</sub> N <sub>2</sub> O <sub>4</sub>	54.55	53.95	3.66	3.58	12.72	12.56

[a] PE = petroleum ether. [b] Molar ratio of dichloroglyoxime to dipolarophile 1:2. [c] Yield based on the dipolarophile used. [d] On the basis of **4a** used. [e] Molar ratio of dichloroglyoxime to dipolarophile 1:1. [f] Based on the total amount of silyl enol ethers **6** (88%) and **7** (12%). [g] On the basis of **11** used.

Table II  
Spectral Data of Prepared Compounds **4a**, **5a-d**, **8**, **9**, **11** and **12**

Compound	<sup>1</sup> H NMR (Deuteriochloroform) (δ ppm)	Mass Spectra (relative intensity)	IR (nujol) cm <sup>-1</sup>
<b>4a</b>	0.12 (s, OSiMe <sub>3</sub> , 18 H), 1.03-2.52 (m, 16 H), 2.95-3.28 (m, 2 H)	424 (M <sup>+</sup> , 36), 406 (31), 379 (4), 335 (M- OSiMe <sub>3</sub> , 6), 319 (14), 317 (11), 196 (12), 170 (17), 75 (100), 73 (77), 45 (23)	1110 (Si-O-C)
<b>5a</b>	1.53-1.97 (m, 8 H), 2.38-2.82 (m, 8 H)	224 (M <sup>+</sup> , 19), 216 (4), 215 (3), 189 (16), 161 (100), 146 (43), 133 (20), 132 (16), 122 (28)	1630
<b>5b</b>	1.37 (s, 18 H), 6.43 (s, 2 H)	248 (M <sup>+</sup> , 28), 233 (M- 15, 100), 219 (3), 205 (3), 191 (8), 163 (M- Me <sub>3</sub> C-CO, 2), 98 (11), 83 (20), 57 (21)	3130, 1650, 1580
<b>5c</b>	2.26 (s, 6 H), 2.79 (s, CH <sub>3</sub> CO-, 6 H)	248 (M <sup>+</sup> , 2), 247 (2), 233 (10), 220 (1), 205 (M- CH <sub>3</sub> CO, 7), 163 (11), 121 (6), 43 (100)	1670, 1590
<b>5d</b>	1.43 (t, J = 7 Hz, 6 H), 2.78 (s, 6 H), 4.37 (q, J = 7 Hz, 4 H)	308 (M <sup>+</sup> , 1), 293 (1), 279 (1), 234 (3), 206 (3), 191 (5), 135 (16), 73 (11), 57 (16), 43 (100)	1725, 1605 [a]
<b>8</b>	2.17 (s, 6 H), 2.38 (s, 6 H)	192 (M <sup>+</sup> , 10), 177 (4), 149 (15), 107 (11), 96 (9), 70 (11), 55 (42), 54 (44), 43 (100)	1630, 1600
<b>9</b>	1.34 (t, J = 7.5 Hz, 3 H), 2.22 (s, 3 H), 2.40 (s, 3 H), 2.84 (q, J = 7.5 Hz, 2 H), 6.48 (s, 1 H)	192 (M <sup>+</sup> , 16), 177 (3), 163 (17), 149 (7), 135 (8), 96 (13), 70 (23), 68 (44), 55 (31), 54 (39), 43 (100), 29 (72)	3130, 1628, 1600, 1590
<b>11</b>	2.31 (s, 6 H), 3.30-3.58 (m, 4 H), 4.85-5.23 (m, 2 H)	224 (M <sup>+</sup> , 3), 181 (3), 139 (2), 97 (5), 95 (7), 81 (8), 70 (13), 55 (26), 43 (100), 28 (70)	1713, 1560
<b>12</b>	2.71 (s, 6 H), 7.43 (s, 2 H)	220 (M <sup>+</sup> , 1), 205 (6), 191 (2), 177 (1), 149 (2), 135 (4), 97 (12), 95 (12), 81 (20), 69 (25), 55 (38), 43 (41), 29 (100)	

[a] Liquid film.

with deuteriochloroform as the solvent on a Varian A60-A spectrometer, with tetramethylsilane as the internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6L spectrometer. The ionization energy was maintained at 70 eV. Petroleum ether refers to the fraction of b.p. 40-60°. Earlier reported methods were used for the preparation of compounds **3a**, **3b**, **6**, **7** [8], **3c** [9], **3d** [10].

General Procedure for the Cycloadditions of Cyanogen *N,N'*-Dioxide (**2**) with Dipolarophiles **3a-d**, **6**, **7**, and **10**. Preparation of Compounds **4a**, **5d**, and **11**.

To a stirred and ice-cooled solution of dichloroglyoxime (**1**) (0.785 g, 5 mmoles) and the appropriate dipolarophile **5a,c,d**, **6**, **7**, **10** (10 mmoles) in dry ether (30 ml) was added a solution of triethylamine (1.4 ml, 10 mmoles) in dry ether (20 ml) during 1 hour. The reaction mixture was then stirred at room temperature for further 12 hours. The precipitated triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure.

The reaction of compound **5b** (0.86 g, 5 mmoles) with dichloroglyoxime (0.785 g, 5 mmoles) was also carried out according to the general method.

In the case of the reaction between compounds **3a** and **1**, the residue obtained after the filtration of triethylamine hydrochloride and concentration of the filtrate, was chromatographed on silica gel, using methylene chloride as eluant. The fractions eluted first was found to be compound **4a** (Tables I, II).

Column chromatography of the mixture obtained from the reaction between **3d** and **1** under conditions similar to those described above, afforded instead of the expected compound **4d**, 3,3'-biisoxazole **5d** as an oil (Tables I, II). No trimethylsilyloxy-derivatives were detected in the eluted fractions, as it was indicated by <sup>1</sup>H-nmr spectroscopy.

In the case of the reaction between compounds **10** and **1**, after filtration of triethylamine hydrochloride the filtrate was concentrated to a small volume to give crystals of compound **11** (Tables I, II).

In all other cases the reaction mixture after filtration of triethylamine hydrochloride was concentrated under reduced pressure and the residue was used for the preparation of the corresponding 3,3'-biisoxazoles.

Preparation of 3,3'-Biisoxazoles **5b-c**, **8** and **9**. General Procedure.

To a solution of the above described residue, obtained from the reactions of **1** with dipolarophiles **3b**, **3c**, **8** or **9** in methanol (15 ml) was added 10% hydrochloric acid (5 ml) and the reaction mixture was heated under reflux for 10 minutes. The cooled reaction mixture was diluted with water (20 ml) and extracted with chloroform. The organic layer was washed with water, dried (sodium sulfate), the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel. The column was eluted with petroleum ether-ethyl acetate (3:1) to give the corresponding 3,3'-biisoxazoles **5b**, **5c**, **8** and **9** (Tables I, II). Compound **4a** was similarly transformed into compound **5a**.

Preparation of 5,5'-bis(Acetyl)-3,3'-biisoxazole (**12**).

To a solution of compound **11** (40 mg, 0.18 mmole) in dry benzene (10 ml) was added  $\gamma$ -manganese dioxide (0.208 g, 1.78 mmoles) and the mix-

ture was heated at reflux for 24 hours. The inorganic precipitates were filtered off and the filtrate was concentrated to a small volume to give crystals of compound **12** (13 mg, 32%) (Tables I, II).

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