

## [1]. Investigations on the Synthesis of Tricyclic 1,5-Benzoxazepines

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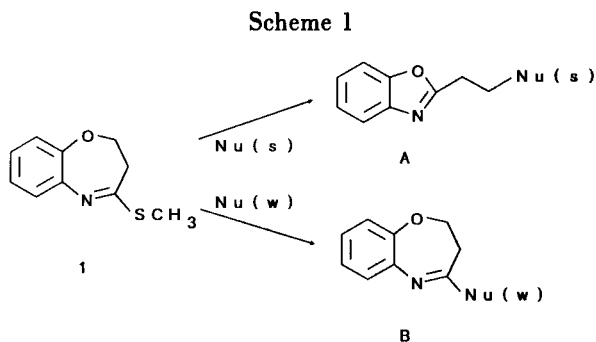
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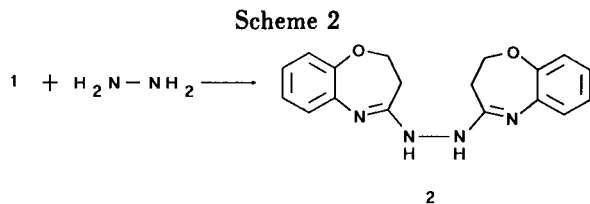
The reaction of methylthiolactim **1** with weak basic *N*-nucleophiles led to the substituted benzoxazepines **2**, **3** and **6a-d**, respectively. Compound **4** was obtained by condensation of **3** with carbonyldiimidazole, whereas **6a-d** were transformed thermally into the triazolobenzoxazepines **7a-d**. Treatment of **6b** with thionyl chloride afforded **8**. Compound **9** directly was obtained from **1** with anthranilic acid.

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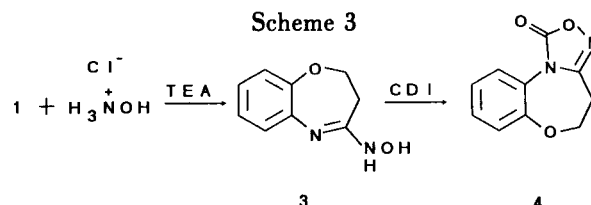
Recently we could show [2], that activated 1,5-benzoxazepine derivatives undergo ring contraction to substituted 2-ethylbenzoxazoles **A** with strong basic nucleophiles (e.g. 1-methylpiperazine). In this paper we investigated, if reaction of the precursor **1** with weak basic *N*-nucleophiles leads to the substituted 1,5-benzoxazepines **B** (Scheme 1). Selected educts would enable the synthesis of tricyclic ring systems.



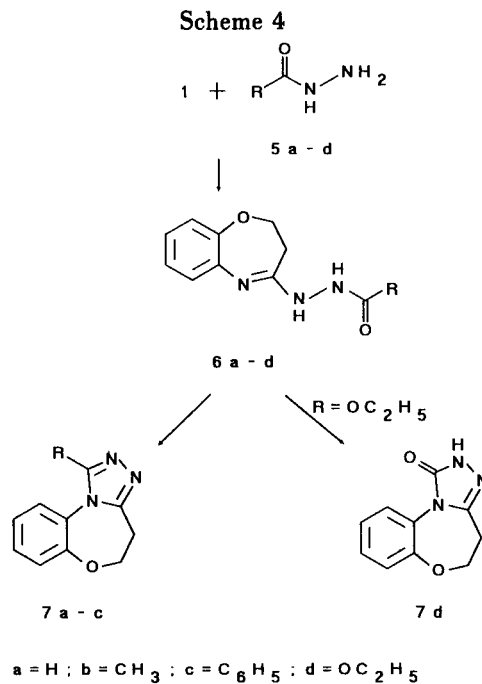
Tentative reaction of methylthiolactim **1** with hydrazine hydrate led to a compound, which <sup>1</sup>H nmr data showed two triplets at 2.65 and 4.37 ppm for the CH<sub>2</sub>-CH<sub>2</sub> unit, respectively. The chemical shift at 4.37 ppm shows the presence of a phenoylether structure and therefore the retention of the seven membered ring system. In the spectrum of the corresponding benzoxazole derivative signals for the CH<sub>2</sub>-CH<sub>2</sub> unit would appear at approximative 2.7-3.4 ppm (see [3]). The molecular weight (M<sup>+</sup> = 322) indicates structure **2** for the isolated compound (Scheme 2). With the less reactive 2,3-Dihydro-1,5-benzoxazepine-4(5*H*)-thione [2] disubstitution of hydrazine also occurred.



Similarly, with hydroxylamine hydrochloride in presence of triethylamine (TEA) compound **3** was obtained, which structure was elucidated by characteristic data (<sup>1</sup>H nmr: CH<sub>2</sub>-CH<sub>2</sub> unit = 2.67 and 4.38 ppm; ms: 146 = M<sup>+</sup>-NHOH). Treatment of **3** with carbonyldiimidazole afforded the oxadiazolo-anellated 1,5-benzoxazepine **4** (Scheme 3).



Under mild conditions reaction of **1** with carbonylhydrazides **5a-c** led to the substitution products **6a-c**, whereas the formation of **6d** occurred by heating a mixture of **1** and **5d**. Refluxing of **6a-d** in toluene with catalytic amounts of glacial acetic acid gave the corresponding tricyclic compounds **7a-c** and **7d**, respectively (Scheme 4).



Besides the cyclisation reactions, described above, **6b** was also treated with thionyl chloride to give the S-containing [d]-annelated benzoxazepine **8**. The tetracyclic compound **9** was obtained by reaction of **1** with anthranilic acid in an one-step procedure (Figure 1).

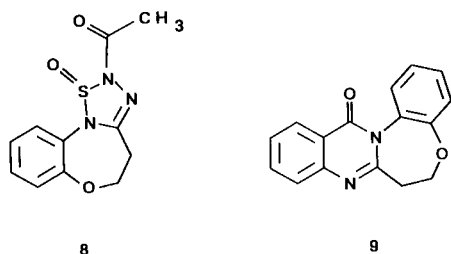


Figure 1

Our investigations showed, that reaction of **1** with weak basic *N*-nucleophiles led to substitution instead of ring contraction. The obtained intermediates are valuable precursors for the formation of polycyclic [d]-annelated 1,5-benzoxazepines.

## EXPERIMENTAL

All melting points are measured with a Kofler Hot-stage apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-311 instrument (70 eV) and <sup>1</sup>H nmr spectra on a Varian EM 390 spectrometer (90 MHz) using TMS as internal standard in deuteriochloroform unless otherwise stated.

### *N,N'*-Bis-(2,3-dihydro-1,5-benzoxazepin-4-yl)hydrazine (**2**).

The solution of hydrazine hydrate (1.5 ml) in ethanol (10 ml) was treated dropwise with a solution of **1** (1.93 g, 10 mmoles) or 2,3-dihydro-1,5-benzoxazepine-4(5*H*)-thione (1.79 g, 10 mmoles) in ethanol (150 ml) at 20°. After stirring for 30 minutes the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was recrystallized from ethanol to give 0.72 g (45%) of **2** as white crystals, mp 170-172°; ms: *m/z* 322 (*M*<sup>+</sup>, 13%), 214 (100%); <sup>1</sup>H nmr: δ 2.65 (t, *J* = 6 Hz, 4H, 2 CH<sub>2</sub>), 4.37 (t, *J* = 6 Hz, 4H, 2 OCH<sub>2</sub>), 4.96 (s-broad, 2H, 2 NH).

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.32; H, 5.82; N, 17.18.

### *N*-(2,3-Dihydro-1,5-benzoxazepin-4-yl)hydroxylamine (**3**).

To a solution of **1** (1.93 g, 10 mmoles) and hydroxylamine hydrochloride (0.76 g, 11 mmoles) in dry ethanol (30 ml) a solution of triethylamine (1.11 g, 11 mmoles) in dry ethanol (5 ml) was added. After stirring for 16 hours at 20° the solvent was evaporated and the residue was recrystallized from a 1:1 mixture of ethyl acetate/petroleum ether (60-80°) to give 1.69 g (95%) of **3** as white crystals, mp 139-141°; ms: *m/z* 178 (*M*<sup>+</sup>, 100%), 146 (*M*<sup>+</sup>-NHOH, 31%); <sup>1</sup>H nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 2.67 (t, *J* = 6 Hz, 2H, CH<sub>2</sub>), 4.38 (t, *J* = 6 Hz, 2H, OCH<sub>2</sub>), 6.93-7.06 (m, 4H, arom), 7.41 (s-broad, 2H, NH, OH).

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.42; H, 5.70; N, 15.46.

### 4,5-Dihydro-1*H*-[1,2,4]oxadiazolo[3,4-*d*][1,5]benzoxazepin-1-one (**4**).

The solution of **3** (1.78 g, 10 mmoles) in dry THF (50 ml) was treated with carbonyldiimidazole (1.78 g, 11 mmoles). After heating for 1 hour the solvent was removed under reduced pressure. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was recrystallized from petroleum ether (50-70°) to give 0.63 g (31%) of **4** as white crystals, mp 108-109°; ms: *m/z* 204 (*M*<sup>+</sup>, 90%), 51 (100%); <sup>1</sup>H nmr: δ 3.00 (t, *J* = 7 Hz, 2H, CH<sub>2</sub>), 4.39 (t, *J* = 7 Hz, 2H, OCH<sub>2</sub>), 7.20-7.78 (m, 4H, arom).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.86; H, 4.01; N, 13.75.

### General Procedure for the Formation of *N'*-(2,3-Dihydro-1,5-benzoxazepin-4-yl)carbohydrazides **6a-d**.

The solution of **1** (1.93 g, 10 mmoles) and **5** (11 mmoles) in ethanol (50 ml) was stirred for 4 hours at 20° (**5d**: 3 hours, reflux). After addition of water (30 ml) the mixture was cooled at 5°. The precipitate was filtered off and recrystallized.

### *N'*-(2,3-Dihydro-1,5-benzoxazepin-4-yl)formohydrazide (**6a**).

From formohydrazide (**5a**, 0.66 g) 1.91 g (93%) of **6a** was obtained as white crystals after recrystallization from THF/petroleum ether (50-70°), mp 110-112°; ms: *m/z* 205 (*M*<sup>+</sup>, 2%), 60 (100%); <sup>1</sup>H nmr: δ 3.25 (t, *J* = 6.5 Hz, 2H, CH<sub>2</sub>), 4.59 (t, *J* = 6.5 Hz, 2H, OCH<sub>2</sub>), 7.17-7.55 (m, 4H, arom), 8.53 (s, 1H, CHO), 8.70 (s-broad, 1H, NH), 10.03 (s-broad, 1H, NH).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.40; H, 5.39; N, 20.35.

### *N'*-(2,3-Dihydro-1,5-benzoxazepin-4-yl)acetohydrazide (**6b**).

From acetohydrazide (**5b**, 0.81 g) 1.80 g (82%) of **6b** was obtained as white crystals after recrystallization from diluted ethanol, mp 149-151°; ms: *m/z* 219 (*M*<sup>+</sup>, 5%), 201 (*M*<sup>+</sup>-H<sub>2</sub>O, 3%), 43 ([CH<sub>3</sub>CO]<sup>+</sup>, 26%); <sup>1</sup>H nmr (trifluoroacetic acid): δ 2.42 (s, 3H, CH<sub>3</sub>), 3.39 (t, *J* = 6 Hz, 2H, CH<sub>2</sub>), 4.91 (t, *J* = 6 Hz, 2H, OCH<sub>2</sub>), 7.28-7.57 (m, 4H, arom).

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.15; H, 5.99; N, 19.17.

### *N'*-(2,3-Dihydro-1,5-benzoxazepin-4-yl)benzohydrazide (**6c**).

From benzohydrazide (**5c**, 1.50 g) 2.53 g (90%) of **6c** was obtained as white crystals after recrystallization from ethanol, mp 178°; ms: *m/z* 281 (*M*<sup>+</sup>, 41%), 253 (*M*<sup>+</sup>-H<sub>2</sub>O, 31%), 173 (100%); <sup>1</sup>H nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 2.67 (t, *J* = 6 Hz, 2H, CH<sub>2</sub>), 4.43 (t, *J* = 6 Hz, 2H, OCH<sub>2</sub>), 6.90-7.10 (m, 4H, arom), 7.35-7.58 (m, 3H, arom), 7.80-8.01 (m, 2H, arom), 8.66 (s-broad, 1H, NH), 10.16 (s-broad, 1H, NH).

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.12; H, 5.38; N, 14.93.

### Ethyl 3-(2,3-Dihydro-1,5-benzoxazepin-4-yl)carbazate (**6d**).

From ethyl carbazate (**5d**, 1.14 g) 2.44 g (98%) of **6d** was obtained as white crystals after recrystallization from diluted ethanol, mp 172°; ms: *m/z* 249 (*M*<sup>+</sup>, 17%), 203 (*M*<sup>+</sup>-C<sub>2</sub>H<sub>5</sub>O, 49%), 146 ([dihydrobenzoxazepinyl]<sup>+</sup>, 100%); <sup>1</sup>H nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 1.25 (t, *J* = 7 Hz, 3H, CH<sub>3</sub>), 2.67 (t, *J* = 6 Hz, 2H, CH<sub>2</sub>), 4.17 (qu, *J* = 7 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.40 (t, *J* = 6 Hz, 2H, OCH<sub>2</sub>), 6.93-7.05 (m, 4H, arom), 8.29 (s-broad, 1H, NH).

*Anal.* Calcd. for  $C_{12}H_{15}N_3O_3$ : C, 57.82; H, 6.07; N, 16.86. Found: C, 57.86; H, 6.10; N, 16.74.

General Procedure for the Formation of 4,5-Dihydro[1,2,4]triazolo[3,4-*d*]1,5]benzoxazepines **7a-d**.

The mixture of **6** (10 mmoles) and glacial acetic acid (1 ml) in toluene (250 ml) was refluxed for 3 hours. After cooling the solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic layer was separated, dried and concentrated *in vacuo*. The crude product was purified by recrystallization.

4,5-Dihydro[1,2,4]triazolo[3,4-*d*]1,5]benzoxazepine (**7a**).

From **6a** (2.05 g) 1.12 g (60%) of **7a** was obtained as white crystals after recrystallization from diluted ethanol, mp 154°; ms: m/z 187 ( $M^+$ , 45%), 60 (100%);  $^1H$  nmr:  $\delta$  3.32 (t, J = 6.5 Hz, 2H,  $CH_2$ ), 4.61 (t, J = 6.5 Hz, 2H,  $OCH_2$ ), 7.22-7.57 (m, 4H, arom), 8.57 (s, 1H, H-1).

*Anal.* Calcd. for  $C_{10}H_9N_3O$ : C, 64.16; H, 4.85; N, 22.45. Found: C, 64.03; H, 4.81; N, 22.23.

4,5-Dihydro-1-methyl[1,2,4]triazolo[3,4-*d*]1,5]benzoxazepine (**7b**).

From **6b** (2.19 g) 1.77 g (98%) of **7b** was obtained as white crystals after recrystallization from methanol, mp 145-146°; ms: m/z 201 ( $M^+$ , 100%);  $^1H$  nmr:  $\delta$  2.54 (s, 3H,  $CH_3$ ), 3.10 (t, J = 6 Hz, 2H,  $CH_2$ ), 4.55 (t, J = 6 Hz, 2H,  $OCH_2$ ), 7.26-7.43 (m, 4H, arom).

*Anal.* Calcd. for  $C_{11}H_{11}N_3O$ : C, 65.66; H, 5.51; N, 20.88. Found: C, 65.56; H, 5.54; N, 20.77.

4,5-Dihydro-1-phenyl[1,2,4]triazolo[3,4-*d*]1,5]benzoxazepine (**7c**).

From **6c** (2.81 g) 2.10 g (80%) of **7c** was obtained as white crystals after recrystallization from a 1:1 mixture of ethyl acetate/*n*-hexane, mp 168°; ms: m/z 263 ( $M^+$ , 100%);  $^1H$  nmr:  $\delta$  3.14 (t, J = 6 Hz, 2H,  $CH_2$ ), 4.60 (t, J = 6 Hz, 2H,  $OCH_2$ ), 6.77-7.54 (m, 9H, arom).

*Anal.* Calcd. for  $C_{16}H_{13}N_3O$ : C, 72.99; H, 4.98; N, 15.96. Found: C, 72.88; H, 5.14; N, 15.84.

4,5-Dihydro[1,2,4]triazolo[3,4-*d*]1,5]benzoxazepin-1(2*H*)-one (**7d**).

From **6d** (2.49 g) 1.77 g (87%) of **7d** was obtained as white crystals after recrystallization from petroleum ether (50-70°), mp 227°; ms: m/z 203 ( $M^+$ , 100%), 146 ([dihydrobenzoxazepinyl] $^+$ , 41%);  $^1H$  nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide):  $\delta$  2.95 (t, J = 6.5 Hz, 2H,  $CH_2$ ), 4.57 (t, J = 6.5 Hz, 2H,  $OCH_2$ ), 7.26-7.56 (m, 3H, arom), 7.73-7.93 (m, 1H, H-10).

*Anal.* Calcd. for  $C_{10}H_9N_3O_2$ : C, 59.11; H, 4.46; N, 20.68. Found: C, 58.96; H, 4.59; N, 20.46.

2-Acetyl-4,5-dihydro-2*H*-[1,2,3,5]thiatriazolo[4,5-*d*]1,5]benzoxazepine 1-Oxide (**8**).

The solution of **6b** (2.19 g, 10 mmoles) in thionyl chloride (30 ml) was stirred for 20 hours at 20°. After concentration *in vacuo* the residue was recrystallized from ethanol to give 1.78 g (67%) of **8** as white crystals, mp 188°; ms: m/z 265 ( $M^+$ , 11%), 146 (100%), 43 ([ $CH_3CO$ ] $^+$ , 72%);  $^1H$  nmr:  $\delta$  2.41 (s, 3H,  $CH_3$ ), 2.95 (t, J = 7 Hz, 2H,  $CH_2$ ), 4.47 (t, J = 7 Hz, 2H,  $OCH_2$ ), 7.18-7.35 (m, 3H, arom), 7.45-7.57 (m, 1H, H-10).

*Anal.* Calcd. for  $C_{11}H_{11}N_3O_3S$ : C, 49.81; H, 4.18; N, 15.84. Found: C, 49.75; H, 4.22; N, 15.77.

6,7-Dihydro-13*H*-quinazolino[2,3-*d*]1,5]benzoxazepin-13-one (**9**).

The solution of **1** (1.93 g, 10 mmoles) and anthranilic acid (1.37 g, 10 mmoles) in dry ethanol (70 ml) was refluxed for 20 hours. The solvent was removed under reduced pressure and the crude product was recrystallized from a 9:1 mixture of water/ethanol to give 1.47 g (56%) of **9** as white crystals, mp 159-161°; ms: m/z 264 ( $M^+$ , 100%);  $^1H$  nmr:  $\delta$  2.89-2.98 and 3.03-3.18 (2 m, 2 x 1H,  $CH_2$ ), 4.22-4.30 and 4.71-4.83 (2 m, 2 x 1H,  $OCH_2$ ), 7.31-7.65 (m, 4H, arom), 7.68-7.84 (m, 3H, arom), 8.31-8.35 (m, 1H, H-1).

*Anal.* Calcd. for  $C_{16}H_{12}N_2O_2$ : C, 72.71; H, 4.58; N, 10.60. Found: C, 72.86; H, 4.94; N, 10.32.

## REFERENCES AND NOTES

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- [2] H. Bartsch and Th. Erker, *Liebigs Ann. Chem.*, 795 (1988).
- [3] H. Bartsch and Th. Erker, *Arch. Pharm. (Weinheim)*, in press.