Studies on the Chemistry of 1,4-Oxazines. 18 [1]. Synthesis of Tricyclic 1,4-Benzoxazines *via* Nucleophilic Substitution of Activated Precursors

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Received July 1, 1988

Starting from activated benzoxazines **1** and **2** new synthetic pathways to the tricyclic compounds **4**, **9**, **12** and **16** are described. Reaction of the hydrazides **17a,b** with thionylchloride leads to the novel thiatriazolobenzoxazines **18a,b**.

J. Heterocyclic Chem., **26**, 205 (1989).

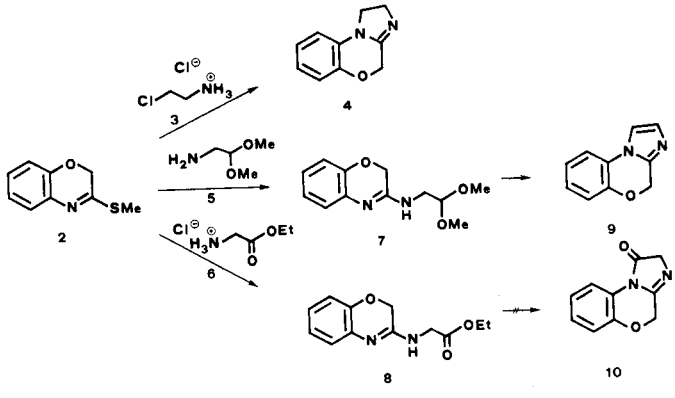
In course of our investigations concerning the synthesis of tricyclic 1,4-benzoxazines [1,2,3] we were interested in a facile access to various [c]-anellated derivatives of this ring system.

Starting from the readily available benzoxazines **1** [4] and **2** [5] reaction with several nucleophiles should lead to the corresponding substitution products, which then should be converted into the tricyclic target compounds.

The synthesis of imidazo[2,1-*c*][1,4]benzoxazines is reported twice in the literature. Whereas from 2-aminophenol and dimethyl acetylenedicarboxylate in several steps the corresponding dicarboxylic acid derivative was obtained [6], reaction of 3-aminobenzoxazine with methyl bromoacetylcarbamate led to a tricyclic carbamate [7].

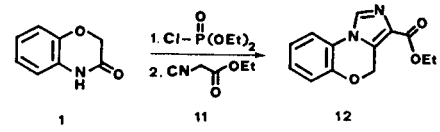
We intended to prepare this ring system in an easy manner starting from **2**. Reaction with **3** yielded the tricycle **4** in one step, whereas **2** with **5** and **6** gave the substitution products **7** and **8**. Attempts to convert **7** and **8** into the tricycles **9** and **10** was only successful with **7**.

Scheme 1



The isomeric imidazo[5,1-*c*][1,4]benzoxazine **12** was obtained from the lactam **1** after activation with diethyl chlorophosphate and successive treatment with ethyl isocyanoacetate (**11**).

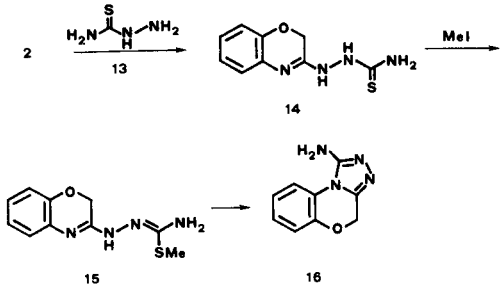
Scheme 2



It is well known, that methylthiolactime **2** with carbohydrazides yields acylhydrazido substituted benzoxazines [8,9], which can be cyclised to the corresponding [1,2,4]triazolo[3,4-*c*][1,4]benzoxazines [9]. Therefore we expected, that reaction with thiosemicarbazide (**13**) - the hydrazide of thiocarbamic acid - also will lead to the tricyclic ring system.

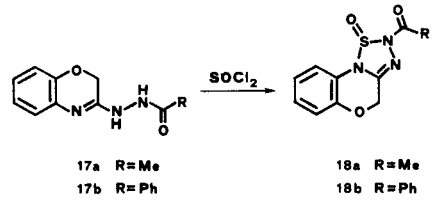
From **2** and **13** the intermediate **14** was obtained. Thiomethylation gave the activated compound **15**, which could be cyclised in acidic medium to the amino substituted triazolobenzoxazine **16**.

Scheme 3



The *N*-substituted hydrazides **17a,b** [8] are not only useful as precursors for the synthesis of triazolobenzoxazines *via* an intramolecular cyclisation reaction. They also could treated with thionylchloride to give in an intermolecular ring formation the *S*-containing [c]-anellated benzoxazines **18a,b**.

Scheme 4



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 nmr spectra on a Bruker AC 80 spectrometer (80 MHz) using TMS as internal standard in deuteriochloroform unless otherwise stated. Ir spectra (potassium bromide) were obtained on a Jasko IRA-1 instrument.

2,4-Dihydro-1*H*-imidazo[2,1-*c*][1,4]benzoxazine (**4**).

To the solution of **2** (1.79 g, 10 mmoles) and **3** (2.32 g, 20 mmoles) in dry ethanol (50 ml), triethylamine (2.02 g, 20 mmoles) was added and the mixture was refluxed for 8 hours. After evaporation of ethanol the residue was partitioned between dichloromethane and water. The organic layer was separated, dried with sodium sulfate, filtered and concentrated *in vacuo*. Recrystallization from petroleum ether (60-80°) yielded 1.17 g (67%) of **4** as white crystals, mp 87°; ms: m/z 174 (M^+, 100%), 173 (M^+ - 1, 56%); nmr: δ 3.54-4.24 (m, 4H, 2 CH_2), 4.72 (s, 2H, OCH_2), 6.48-7.06 (m, 4H, aromat).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.72; H, 5.80; N, 16.07.

N-(2*H*-1,4-Benzoxazin-3-yl)aminoacetaldehyde Dimethyl Acetal (**7**).

The solution of **2** (1.79 g, 10 mmoles) and **5** (1.58 g, 15 mmoles) in dry ethanol (50 ml) was refluxed for 8 hours. The solvent was removed under reduced pressure. After distillation 1.68 g (71%) of **7** were obtained as colourless oil, bp 180°, 0.001 mm Hg; ms: m/z 236 (M^+, 24%), 205 (M^+ -OCH_3, 14%), 204 (M^+ - OCH_3 - H, 17%), 173 (M^+ - 2 OCH_3 - H, 45%), 75 ($[C_3H_7O_2]^+$, 100%); nmr: δ 3.42 (s, 6H, 2 OCH_3), 3.63 (d, J = 6 Hz, 2H, NCH_2), 4.40 (s, 2H, OCH_2), 4.54 (t, J = 6 Hz, 1H, CH), 6.66-7.25 (m, 4H, aromat).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.81; H, 6.89; N, 11.48.

Ethyl *N*-(2*H*-1,4-Benzoxazin-3-yl)aminoacetate (**8**).

To the solution of **2** (1.79 g, 10 mmoles) and **6** (2.10 g, 15 mmoles) in dry ethanol (50 ml) triethylamine (1.52 g, 15 mmoles) was added. After stirring for 6 hours at 20° the solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated, dried with sodium sulfate, filtered and concentrated *in vacuo*. Recrystallization from ethanol yielded 1.71 g (73%) of **8** as white crystals, mp 137°; ms: m/z 234 (M^+, 90%), 161 (M^+ - $COOC_2H_5$, 100%); nmr: δ 1.27 (t, J = 8 Hz, 3H, CH_3), 4.21 (s, 2H, NCH_2), 4.23 (q, J = 8 Hz, 2H, OCH_2), 4.39 (s, 2H, OCH_2), 6.72-7.18 (m, 4H, aromat).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.43; H, 6.04; N, 11.88.

4*H*-Imidazo[2,1-*c*][1,4]benzoxazine (**9**).

The solution of **7** (2.36 g, 10 mmoles) in methanol (25 ml) and concentrated hydrochloric acid (25 ml) was refluxed for 2 hours. After concentration *in vacuo* the residue was dissolved in dichloromethane, washed with 5% sodium hydrogen carbonate solution and water, dried over sodium sulfate, filtered, and the solvent was evaporated. Recrystallization from petroleum ether (60-80°) yielded 1.07 g (62%) of **9** as white needles, mp 105°; ms: m/z 172 (M^+, 100%); nmr: δ 5.27 (s, 2H, OCH_2), 7.03-7.36 (m, 6H, H-1, H-2, H-6 to H-9).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.62; H, 4.71; N, 16.16.

Ethyl 4-*H*-Imidazo[5,1-*c*][1,4]benzoxazin-3-carboxylate (**12**).

The solution of **1** (1.49 g, 10 mmoles) and potassium *t*-butoxide (1.12 g, 10 mmoles) in dry DMF (30 ml) was cooled to 0° under argon. After 10 minutes, diethyl chlorophosphate (3.45 g, 20 mmoles) was added. After additional 5 minutes, a solution of **11** (1.69 g, 15 mmoles) and potassium *t*-butoxide (1.68 g, 15 mmoles) in dry DMF was added. The reaction mixture was stirred at 20° for 15 hours, acidified carefully with acetic acid, diluted with water (40 ml) and poured into ice-water (200 ml). After 30 minutes, the solid was filtered with suction, washed with water, dried and recrystallized from ethyl acetate to yield 1.37 g (56%) of **12** as white crystals, mp 148°; ms: m/z 244 (M^+, 10%), 198 (M^+ -OC_2H_5, 17%), 133 (M^+ - C=N-$CH_2COOC_2H_5$, 100%); nmr: δ 1.31 (t, J = 8 Hz, 3H, CH_3), 4.39 (q, J = 8 Hz, 2H, OCH_2), 5.54 (s, 2H, OCH_2), 7.00-7.57 (m, 4H, aromat), 8.06 (s, 1H, H-1); ir: 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.76; H, 5.04; N, 11.69.

1-(2*H*-1,4-Benzoxazin-3-yl)thiosemicarbazide (**14**).

The solution of **2** (1.79 g, 10 mmoles) and **13** (0.91 g, 10 mmoles) in dry ethanol (40 ml) was refluxed for 4 hours. After cooling, the precipitate was collected and recrystallized from ethanol to give 1.89 g (85%) of **14** as white crystals, mp 198°; ms: m/z 222 (M^+, 59%), 205 (M^+ - NH_3, 64%), 189 (M^+ - SH, 24%), 109 ([2-aminophenol]$^+$, 100%); nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 4.45 (s, 2H, OCH_2), 6.79-6.97 (m, 4H, aromat), 7.18 (s-broad, 1H, NH), 7.29 (s-broad, 1H, NH), 9.96 (s-broad, 1H, NH), 10.06 (s-broad, 1H, NH).

Anal. Calcd. for $C_9H_{10}N_4OS$: C, 48.63; H, 4.54; N, 25.21. Found: C, 48.54; H, 4.55; N, 25.00.

1-(2*H*-1,4-Benzoxazin-3-yl)-*S*-methylisothiosemicarbazide (**15**).

To a suspension of sodium hydride (0.40 g, 80%) in dry THF (10 ml) the solution of **14** (2.22 g, 10 mmoles) in dry THF (20 ml) was dropped. After 15 minutes iodomethane (2.13 g, 15 mmoles) in dry THF (10 ml) was added and the mixture was stirred for 2 hours at 20°. After evaporation of THF the residue was partitioned between dichloromethane and water. The organic layer was separated, dried with sodium sulfate, filtered and concentrated *in vacuo*. Recrystallization from ethanol yielded 2.05 g (87%) of **15** as white crystals, mp 144°; ms: m/z 236 (M^+, 27%), 189 (M^+ - SCH_3, 100%); nmr: δ 2.45 (s, 3H, SCH_3), 4.66 (s, 2H, OCH_2), 5.27 (s-broad, 2H, NH_2), 6.65-7.06 (m, 4H, aromat), 8.06 (s-broad, 1H, NH).

Anal. Calcd. for $C_{10}H_{12}N_4OS$: C, 50.83; H, 5.12; N, 23.71. Found: C, 50.83; H, 5.17; N, 23.92.

4*H*-[1,2,4]Triazolo[3,4-*c*][1,4]benzoxazin-1-amine (**16**).

The mixture of **15** (2.36 g, 10 mmoles) and acetic acid (5 ml) in dry ethanol (50 ml) was refluxed for 2 hours. After evaporation of the solvent, the residue was taken up in dichloromethane, washed with 5% sodium hydrogen carbonate solution and water, dried over sodium sulfate and filtered. The solvent was concentrated *in vacuo* and the crude product recrystallized from ethyl acetate to give 1.75 g (93%) of **16** as pale crystals, mp 213°; ms: m/z 188 (M^+, 82%), 159 (100%); nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 5.15 (s, 2H, OCH_2), 5.81 (s-broad, 2H, NH_2), 6.97-7.33 (m, 3H, aromat), 7.66-7.90 (m, 1H, H-9).

Anal. Calcd. for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.05; H, 4.28; N, 29.40.

General Procedure for the Formation of Thiatriazolobenzoxazines **18a,b**.

The suspension of compounds **17a,b** [8] (10 mmoles) in thionylchloride (10 ml) was stirred for 8 hours at 20°. After concentration *in vacuo* the residue was recrystallized.

2-Acetyl-4*H*-[1,2,3,5]thiatriazolo[4,5-*c*][1,4]benzoxazine 1-Oxide (**18a**).

Compound **17a** (2.05 g) afforded 2.01 g (80%) of **18a** as white crystals, mp (dry methanol) 131°; ms: m/z 251 (M^+, 8%), 209 (M^+ - CH_2CO, 25%), 43 ([CH_3CO]$^+$, 100%); nmr: δ 2.46 (s, 3H, CH_3), 4.98 (s, 2H, OCH_2), 7.08-7.26 (m, 4H, aromat); ir: 1690 (C=O), 1170 cm^{-1} (S=O).

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.80; H, 3.61; N, 16.72. Found: C, 47.58; H, 3.68; N, 16.61.

2-Benzoyl-4*H*-[1,2,3,5]thiatriazolo[4,5-*c*][1,4]benzoxazine 1-Oxide (**18b**).

Compound **17b** (2.67 g) afforded 2.25 g (72%) of **18b** as white crystals, mp (dry 1-butanol) 133°; ms: m/z 313 (M^+, 3%), 105 ([benzoyl]$^+$, 100%); nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 5.06 (s, 2H,

OCH_2), 7.06-7.18 (m, 3H, aromat), 7.36-7.57 (m, 4H, aromat), 8.03-8.18 (m, 2H, aromat); ir: 1650 (C=O), 1160 cm^{-1} (S=O).

Anal. Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.50; H, 3.54; N, 13.41. Found: C, 57.35; H, 3.65; N, 13.15.

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