

# A novel and efficient method for the conversion of a *trans*-hexahydronaphthoxazine to a *cis*-isomer using boron tribromide

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**Abstract**—A novel and efficient method for the conversion of a *trans*-hexahydronaphthoxazine to a *cis*-isomer was achieved in high yield by utilizing boron tribromide in methylene chloride at  $-20\text{ }^{\circ}\text{C}$ .

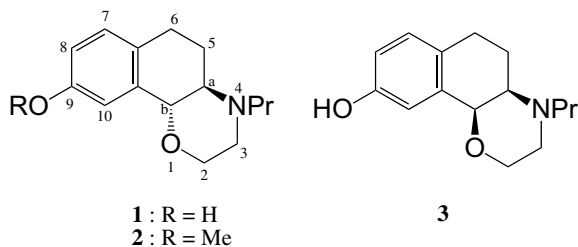
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There is considerable interest in the scientific community regarding the synthesis and use of naphthoxazines. This class of compounds has been found to possess very potent dopamine receptor agonist activity as well as selective modes of action at the D2 receptors.<sup>1</sup> *trans*-4-Propyl-9-hydroxynaphthoxazine **1**, for example, has exhibited therapeutic potential for treatment of Parkinson's disease.<sup>2</sup> Various *cis*-naphthoxazine analogs have been synthesized to facilitate SAR studies and possibly provide compounds with improved biological profiles. Unfortunately, the *cis*-isomers are more difficult to synthesize and are generally prepared from the corresponding tetrahydronaphthyl amino or acetamido tetralone precursors by methods involving laborious separation of *cis*–*trans* mixtures or requiring very harsh conditions and additional transformations.<sup>3</sup> We now wish to report a novel and efficient synthesis of the *cis*-hydroxynaphthoxazine system by treatment of the corresponding

*trans*-methoxy analog with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  at low temperature.

*trans*-4-Propyl-9-methoxynaphthoxazine **2** was readily prepared *via* a highly stereoselective reduction of its amino-1-tetralone precursor as described in the literature.<sup>4</sup> Selective demethylation of methoxynaphthoxazine **2** with 2 equiv of  $\text{BBr}_3$  at  $-20\text{ }^{\circ}\text{C}$  for 2 h in  $\text{CH}_2\text{Cl}_2$  provided, surprisingly and exclusively, the *cis*-hydroxynaphthoxazine **3** in 84% yield and excellent purity without chromatography. No *trans*-isomer could be detected by  $^1\text{H}$  NMR analysis. The *cis*-stereochemistry was established by the presence of a doublet ( $J = 2\text{ Hz}$ , H-10b) in the  $^1\text{H}$  NMR spectrum<sup>5</sup> at 4.37 ppm ( $\text{DMSO}-d_6$ ) or 4.52 ppm ( $\text{CDCl}_3$ ). The ROESY spectrum confirmed that the oxygen and nitrogen protons are indeed *cis* to each other with H-10b showing an NOE to H-4a. It was found that 2 equiv of the boron reagent are necessary to provide the *cis*-naphthoxazine in high yield. Conversion of the *trans*-hydroxynaphthoxazine **1** to the *cis*-hydroxynaphthoxazine **3** was also accomplished in similar fashion and yield. Another boron reagent,  $\text{BCl}_3$ , also provided the *cis*-hydroxynaphthoxazine **3** from the *trans*-methoxynaphthoxazine **2** but in much lower yield (32%, mostly unreacted starting material).

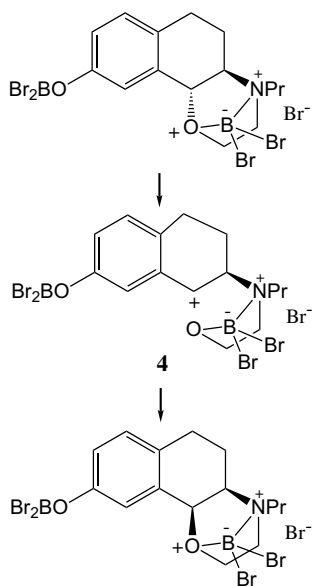
Interestingly, if the HCl salt of the methoxy substrate **2** is treated with 1.1 equiv of  $\text{BBr}_3$ , the expected *trans*-hydroxynaphthoxazine **1** is obtained in 73% yield.<sup>6</sup> Other demethylating agents such as pyridine hydrochloride ( $200\text{ }^{\circ}\text{C}$ , 1 h, 25%) or methionine/methanesulfonic acid ( $23\text{ }^{\circ}\text{C}$ , 44 h, 90%) provided only the *trans*-isomer.



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The *trans*-stereochemistry was verified by a doublet ( $J = 8.7$  Hz, H-10b) in the  $^1\text{H}$  NMR spectrum<sup>7</sup> at 4.11 ppm ( $\text{DMSO}-d_6$ ) or 4.31 ppm ( $\text{CDCl}_3$ ). The ROESY spectrum showed that H-10b has an NOE to H-5 while H-4a has an NOE with H-6 indicating that H-10b and H-4a are *trans* to each other.

Attempts to convert the *cis*-methoxynaphthoxazine isomer to the *trans*-hydroxynaphthoxazine using  $\text{BBr}_3$  were unsuccessful. Apparently, the *cis*-isomer is the more favorable or stable conformation in the presence of  $\text{BBr}_3$ . Since it appears that boron coordination or complexation may play a role in this unique transformation, a possible mechanism for the conversion involves the formation of the carbocation **4**.



In conclusion, we have developed a new and facile method for converting directly and efficiently a *trans*-hexahydronaphthoxazine to a *cis*-isomer. The methodology described also takes advantage of the readily prepared *trans*-methoxy substrate. This discovery, therefore, makes the *cis* series or derivatives of these compounds more synthetically accessible.

## Experimental

*cis*-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphth[1,2-*b*]-[1,4]oxazin-9-ol (**3**). *trans*-Methoxynaphthoxazine **2** (9 g, 34.5 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (180 mL) and the temperature lowered to  $-70^\circ\text{C}$ .  $\text{BBr}_3$  (69 mL of 1 M solution in  $\text{CH}_2\text{Cl}_2$ , 69 mmol) was added so that the internal temperature was below  $-60^\circ\text{C}$ . The reaction mixture was allowed to stir at  $-20^\circ\text{C}$  for 2 h. At this point the reaction was allowed to warm to  $0^\circ\text{C}$  to insure

completeness of reaction. The reaction was then quenched with methanol at  $-20^\circ\text{C}$ . The solvent was removed to provide the HBr salt of the *cis*-hydroxynaphthoxazine, which can be further purified by washing with cold ether (HPLC purity  $>95\%$ ). Treatment of the acid salt with saturated aqueous  $\text{NaHCO}_3$  and extraction with  $\text{CH}_2\text{Cl}_2$  provided, after drying, filtration, and removal of solvent, the *cis*-hydroxynaphthoxazine **3** in 84% yield (7.16 g, HPLC purity  $>95\%$ ). The reaction could also be quenched with saturated aqueous  $\text{NaHCO}_3$  and extracted into  $\text{CH}_2\text{Cl}_2$  or ether to give the free base directly.

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- cis*-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphth[1,2-*b*]-[1,4]oxazin-9-ol (**3**).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.03 (s, 1H), 6.88 (d, 1H,  $J = 7.5$  Hz), 6.79 (d, 1H,  $J = 1.9$  Hz), 6.60 (dd, 1H,  $J = 1.9$  Hz, 7.8 Hz), 4.37 (d, 1H,  $J = 2$  Hz), 3.65 (br d, 1H,  $J = 10.8$  Hz), 3.64 (br t, 1H,  $J = 11.2$  Hz), 2.70–2.81 (m, 2H), 2.30–2.60 (m, 4H), 1.95–2.05 (m, 2H), 1.60–1.69 (m, 1H), 1.4–1.50 (m, 2H), 0.88 (t, 3H,  $J = 7.3$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  154.6, 136.2, 128.4, 126.8, 115.1, 114.7, 74.0, 64.7, 56.9, 55.1, 47.4, 26.3, 19.4, 17.2, 11.9; MS (DCI/ $\text{NH}_3$ )  $m/z$  248 ( $\text{M}+\text{H}$ )<sup>+</sup>.
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- trans*-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphth[1,2-*b*]-[1,4]oxazin-9-ol (**1**).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.07 (s, 1H), 6.8–6.9 (m, 2H), 6.57 (dd, 1H,  $J = 1.9$  Hz, 7.8 Hz), 4.11 (d, 1H,  $J = 8.7$  Hz), 3.95 (br d, 1H,  $J = 10.8$  Hz), 3.74 (br t, 1H,  $J = 11.2$  Hz), 2.63–2.86 (m, 4H), 2.00–2.35 (m, 4H), 1.30–1.55 (m, 3H), 0.90 (t, 3H,  $J = 7.3$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  155.2, 137.2, 128.6, 124.8, 114.0, 111.3, 78.4, 66.6, 62.2, 54.2, 51.9, 26.5, 24.0, 18.6, 11.7; MS (DCI/ $\text{NH}_3$ )  $m/z$  248 ( $\text{M}+\text{H}$ )<sup>+</sup>.