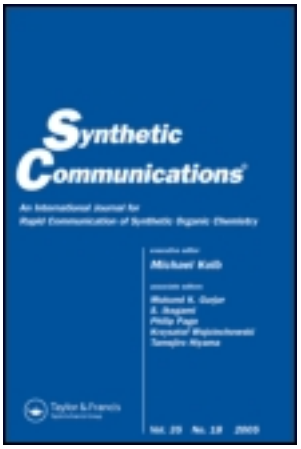

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SYNTHESIS OF CHIRAL NADH ANALOG BASED ON PROLINE TEMPLATE INCLUDING THIOUREA AND NICOTINIC ACID MOIETIES

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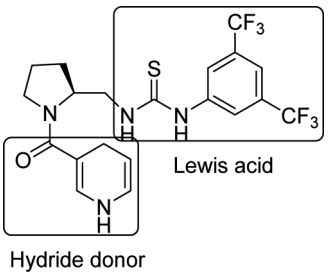
GRAPHICAL ABSTRACT



Abstract *Chiral reductase-mimicking organic molecule built on proline template incorporating a covalently bound NADH mimic via thiourea, and related reducing agent Hantzsch dihydropyridine, was designed. A synthetic path was developed involving interlinking of chiral proline derivatives with thiourea and subsequent coupling reaction with nicotinoyl chloride. The structure of target compound was studied by x–ray, indicating a double H bond with thiourea hydrogens and oxygen O1 of benzylcarbamate fragment. The reduction of benzil and imines was performed.*

Keywords Enantioselective synthesis; NADH analog; proline; reduction

INTRODUCTION

A large number of NADH model compounds have been designed with the aim of mimicking reduction process in vitro for development of new enantioselective reducing agents during recent years.[1] Generally, chiral NADH models have been designed by modifying the dihydropyridine ring or incorporating remote sterically demanding side chains, or a substituent at the reaction center, the C4 position of the dihydropyridine ring.[2] Herein, we report a synthesis of a chiral NADH model compound based on a proline template including thiourea and nicotinic acid

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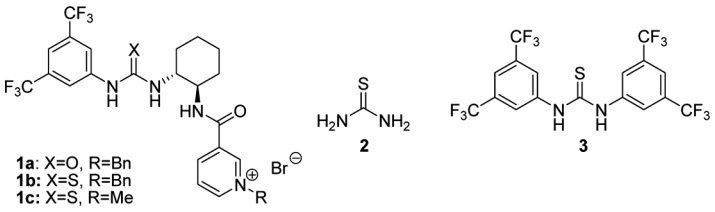


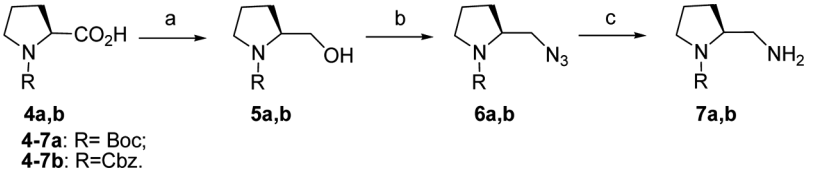
Figure 1. Multifunctional organocatalysts.

moieties. This approach may contribute to a development of new strategies for asymmetric reductions of unsaturated organic compounds. Asymmetric reductions have become an important goal of research carried out in both academic and industrial laboratories because of a constantly increasing demand for enantiomerically pure and biologically active substances.[3] Procuranti and Connon were the first to demonstrate that multifunctional derivatives **1a–c** (Fig. 1) based on (thio)ureas and nicotinic acid moieties were efficient for the reduction of 1,2-diketones.[4] Recently, novel urea and thiourea derivatives have been developed.[5] However, chiral thioureas have not yet been explored as catalysts for asymmetric reduction of prochiral ketones or imines using Hantzsch dihydropyridine ester.

The reduction of benzil (1,2-diphenyl-1,2-ethanedione, PhCOCOPh) by using urea derivative **1b** provided benzoin (2-hydroxy-2-phenylacetophenone) at almost complete conversion yet with only 2% *ee*, and under different conditions enantiomeric excess increased, though with a lesser conversion, proving the product racemization under the reaction conditions. Menche and Arikan reported on the reductive amination of ketones and aldehydes with thiourea **2**; however, subsequent work of Zhang and Schreiner revealed that thiourea does not catalyze the formation of imines though catalyzes its reduction.[6] They developed catalyst **3** (Fig. 1), which was more efficient for the reduction of aldimines compared to thiourea **2**.

RESULTS AND DISCUSSION

We report the synthesis of a chiral coenzyme NADH model based on a chiral thiourea analog built on proline as a chiral organic Lewis acid and involving the nicotinic acid moiety. The general synthesis of the target compound is presented in Scheme 1. The synthesis of chiral protected amines **7a** and **b** starting from proline protected with benzyl carbamate and *tert*-butyl carbamate groups **4a** and **b**,



Scheme 1. Reagents and conditions: (a) (1) $ClCO_2Et$, TEA, −15 °C, (2) $NaBH_4$, THF/H_2O, 0 °C; **5a** (76%), **5b** (80%); (b) (1) TsCl, TEA, THF, Rt, (2) NaN_3, DMF, 80 °C; **6a** (80%), **6b** (78%); (c) **7a**: Pd/C, H_2 (1 atm.), MeOH, Rt (97%), **7b**: Zn, NH_4Cl, $EtOH/H_2O$ (3:1), Rt (90%).

respectively, was accomplished following reported procedures.[7] Compounds **4a** and **b** were converted into alcohols **5a** and **b** via a two-step sequence including the activation of acid with ethyl chloroformate and the following reduction with sodium borohydride. The azides **6a** and **b** were synthesized from alcohols **5a** and **b** in two steps by an activation of the latter with 4-toluenesulfonyl chloride[8] and following substitution with sodium azide. The azide **6a** protected with *tert*-butyl carbamate group was converted into amine **7a** by reduction using palladium on carbon as a catalyst.[9] Meanwhile, a benzyl carbamate protected azide **6b** was reduced with zinc in the presence of ammonium chloride[10] because **6b** was not stable at conditions used for the reduction of **6a** (Scheme 1).

The amines **7a** and **b** were coupled with thioureas **8a** and **b** using an elaborate procedure by mixing amines and appropriate isothiocyanate in dry dichloromethane. The deprotection of the benzyl carbamate group was unsuccessful using several methods (*viz*. by palladium on carbon as a catalyst in methanol, and under the same conditions in acetic acid, as well as by mixing with $BF_3 \cdot Et_2O$ and PhSH at room temperature,[11] either with trimethylsilyl iodide in acetonitrile[12]). The Boc protected derivative **8a**, however, was deprotected smoothly with in situ–generated hydrogen chloride[13] in excellent yield (94%), affording product **9**.[14]

A coupling reaction between amine **9** and nicotinic acid chloride was accomplished with 4-dimethylaminopyridine and *N,N*-diisopropylethylamine to afford **10** in 63% yield.

The structure of **8b** was studied by x-ray analysis, obtaining single crystals from ethanol. It should be noticed that the crystal structure of **8b** (Fig. 2) showed a double

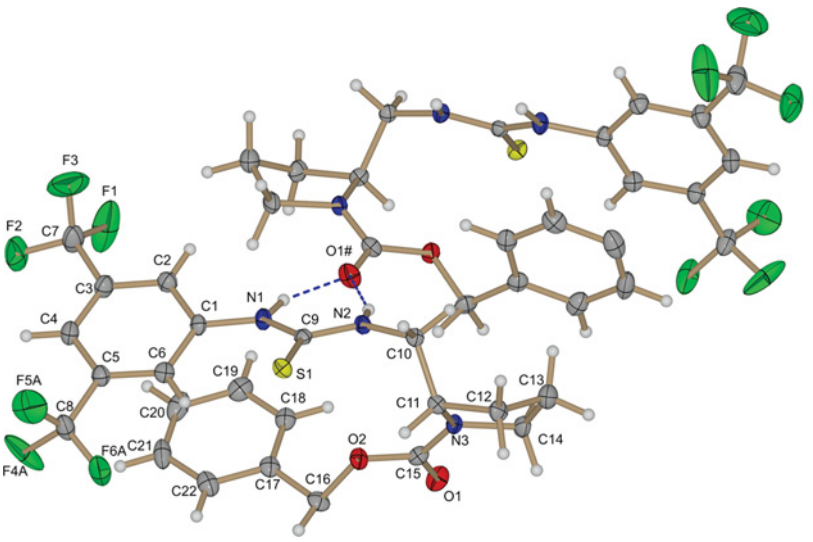
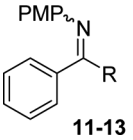


Figure 2. Thermal ellipsoid plot (50% probability level) of **8b** with the hydrogen bonds (dashed line) to the closest neighboring molecule. One of the CF_3 groups is positionally disordered over two sites: only one of these is shown. Hydrogen bonds (Å, °): N1–H1N 0.97(3), H1N O1# 1.98(3), N1 O1# 2.911(2), N1–H1N O1# 160(2), N2–H2N 0.86(2), H2N O1# 2.08(2), N2 O1# 2.910(2), N2–H2N O1# 160(2). #: $x+\frac{1}{2}$, $y-\frac{1}{2}$, $-z+2$.

H bond with thiourea hydrogens and oxygen O1 of the benzylcarbamate fragment. The distances N1 O1# and N2 O1# are 2.911(2) Å and 2.910(2), respectively (#: $x+\frac{1}{2}$, $y-\frac{1}{2}$, $-z+2$). Because of the intermolecular hydrogen bonding, the molecules of **8b** form 1D chains in the direction of the *a* axis.

The synthesized NADH model **10** was examined in the catalytic reduction of benzil by using sodium dithionite as coreductant under the same conditions previously developed.[4] In contrast, it was found that catalyst **10** under these conditions afforded benzoin, though in poor yield, whereas at higher temperature (50 °C) the yield of benzil reduction product increased to 20–30%. However, the product racemization occurred under the reaction conditions. It should be mentioned that the reduction under the same conditions with sodium dithionite entirely could not be ignored.[15]



11-13

11: R= Me
12: R= COPh
13: R= CO_2Me
PMP- 4-methoxyaniline

Further, reduction of imines **11, 12**, and **13** using Hantzsch dihydropyridine ester with **8b** was performed under conditions developed by Menche. The reductions were carried out in dichloromethane at 60 °C in a Schlenk flask. However, the reduction of **11** and **12** did not proceed under these conditions, and only ca 10% conversion was achieved with the substrate **13** after 120 h as estimated by ^{1}H NMR spectroscopy.

In conclusion, we have synthesized a reductase-mimicking chiral NADH analog built on proline framework incorporating a covalently bound thiourea with related reducing agent, Hantzsch dihydropyridine. The reduction of benzil and imines **11–13** was performed by recycling the catalyst **10** in situ using sodium dithionite under basic conditions: however, the reduction products were obtained with rather poor conversion (ca. 30%). This could be explained by the modest catalytic reaction cycles (turnover number was estimated to be ca. 4) and also a nonselective reduction of nicotine acid moiety (change of 1,4-dihydropyridine to an inactive 1,2-dihydro form). The practical exploration of the developed system is complicated because of the eventual racemization of products under the reaction conditions. Further modification of the NADH analogs is in progress.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are not corrected. Infrared (IR) spectra were recorded in KBr pellets on a Perkin-Elmer Spectrum BX spectrometer. Proton and carbon nuclear magnetic resonance spectra were recorded in $CDCl_3$, d_6-acetone, and dimethylsulfoxide (d_6-DMSO) on a Varian XL300 spectrometer, and chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as an internal standard. The mass spectra (positive ion EI) were measured on a dual-sector mass spectrometer using direct inlet. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F254 (Merck) sheets coated

with silica gel, and Kieselgel 60 silica gel (0.040–0.063 mm, Merck) was used for column chromatography. Optical rotations were measured on a polarimeter Polamat-A (Carl Zeiss) at 546 nm.

Toluene and tetrahydrafuran (THF) were distilled from sodium benzophenone. Dichloromethane, chloroform, and acetonitrile were distilled from CaH_2. Dimethylformamide (DMF) was dried over CaH_2 and distilled under reduced pressure.

(S)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(*tert*-butyloxycarbonyl and Carbobenzyloxy Pyrrolidin-2-ylmethyl)thiourea (8a and b)

3,5-Bis(trifluoromethyl)phenyl isothiocyanate (87 µl, 0.48 mmol) was added to a stirred solution of **7a** (100 mg, 0.50 mmol) or **7b** (220 mg, 0.94 mmol) in dry CH_2Cl_2 (10 ml) at room temperature. The reaction mixture was stirred for 12 h under argon. Removing the solvent in vacuo afforded the crude product purified by column chromatography [petroleum ether/ethyl acetate (5:1)]. Removing the solvent in vacuo afforded a white solid.

Compound 8a. Yield 160 mg (74%). $[\alpha]_{546}^{17} = -54.2°$ (1.90, chloroform); mp 55–57 °C; IR (KBr, cm^{-1}): ν 3250, 1665, 1623, 1543, 1278; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.99 (bs, 1H), 8.28 (s, 2H), 7.77 (s, 1H), 3.92–3.79 (m, 1H), 3.57–3.32 (m, 3H), 3.00 (bs, 1H), 2.20–1.81 (m, 2H), 1.49 (s, 9H), 1.31–1.24 (m, 2H); ^{19}F NMR (280 MHz, $CDCl_3$, ppm) δ − 63.36; ^{13}C NMR (100 MHz, d_6-acetone, ppm) δ 180.4, 156.4, 140.3, 131.8, 125.0, 121.6, 117.9, 57.5, 53.4, 47.5, 46.7, 30.8, 28.4, 24.0; HRMS (EI) 471.1415 ($C_{19}H_{23}F_6N_3O_2S$ requires 471.1415).

Compound 8b. Yield 400 mg (89%). $[\alpha]_{546}^{17} = -34.0°$ (2.55, chloroform); mp 125–126 °C; IR (KBr, cm^{-1}): ν 3343, 1654, 1628, 1553, 1276; ^{1}H NMR (300 MHz, d_6-acetone, ppm) δ 8.85 (bs, 1H), 8.40 (m, 2H), 7.76 (s, 1H), 7.42–7.36 (m, 5H), 5.16 (s, 2H), 7.17–4.05 (m, 1H), 3.96–3.50 (m, 5H), 2.13–1.95 (m, 4H); ^{19}F NMR (280 MHz, d_6-acetone, ppm) δ 63.27; ^{13}C NMR (100 MHz, d_6-acetone, ppm) δ 181.7, 156.4, 142.2, 137.4, 131.1, 128.6, 127.9, 123.8, 123.1, 117.0, 66.8, 57.6, 49.5, 46.9, 23.9, 23.0; HRMS (EI) 505.1259 ($C_{22}H_{21}F_6N_3O_2S$ requires 505.1259).

(S)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(pyrrolidin-2-ylmethyl)thiourea Hydrochloride (9)

A solution of **8a** (440 mg, 0.97 mmol) in 10 ml dry CH_2Cl_2 was cooled to 0 °C and 0.46 ml (9.7 mmol) MeOH and 0.69 ml (9.7 mmol) AcCl were added under argon. The mixture was stirred at room temperature for 24 h, and the precipitate was filtered and washed with petroleum ether to yield a white solid **9** (370 mg, 94%). ^{1}H NMR (300 MHz, d_6-DMSO, ppm) δ 9.21 (bs, 1H), 8.94 (bs, 1H), 8.73 (bs, 1H), 8.34 (s, 2H), 7.81 (s, 1H), 3.86–3.84 (m, 3H), 3.25–3.20 (m, 2H), 2.16–1.60 (m, 4H); ^{19}F NMR (280 MHz, d_6-DMSO, ppm) δ −61.91.

Compound 10

A solution of 140 mg (0.34 mmol) of hydrochloride **9**, 73 mg (0.41 mmol) of nicotinoyl chloride hydrochloride, and 10 mg (0.082 mmol) DMAP in 10 ml dry CH_2Cl_2 was cooled to 0 °C. Then 0.24 ml (1.4 mmol) disopropylethyl amine (DIPEA) was added, and the mixture was stirred at room temperature 24 h under argon. Upon completion, the reaction was quenched with a saturated solution of $NaHCO_3$. The organic layer was then diluted with CH_2Cl_2 and was washed with water and brine. The combined organic layer was dried over Na_2SO_4. Filtration and evaporation of the solvent provided the crude product, which was purified by column chromatography (ethyl acetate), and evaporation of solvent in vacuo afforded a white solid **10** (100 mg, 63%), mp 68–70 °C. $[\alpha]_{546}^{17} = -43.6$ (1.15, acetone); ^{1}H NMR (300 MHz, d_6-acetone, ppm) δ 9.71 (bs, 1H), 8.81–8.84 (m, 1H), 8.70–8.72 (m, 1H), 8.34 (s, 2H), 7.98–8.10 (m, 1H), 7.74 (s, 1H), 7.48–7.51 (m, 1H), 4.50–4.63 (m, 1H), 3.45–4.16 (m, 4H), 3.42 (bs, 1H), 1.91–2.40 (m, 4H); ^{19}F NMR (280 MHz, acetone-d_6, ppm) δ 63.82; ^{13}C NMR: (100 MHz, acetone-d_6, ppm) δ 181.7, 169.0, 151.2, 148.6, 142.2, 135.1, 131.5, 123.8, 123.4, 122.9, 116.9, 57.3, 50.4, 46.9, 25.0, 24.8; HRMS (EI) 476.1106 ($C_{20}H_{18}F_6N_4OS$ requires 476.1106).

Reduction of Benzil Using 10

In a flask with a stirring bar, Na_2CO_3 (30 mg, 0.30 mmol), $Na_2S_2O_4$ (50 mg, 0.30 mmol), and a catalytic amount of **10** (5 mg, 0.0075 mmol) were dissolved in water (1.0 ml). Subsequently, a solution of the benzil (30 mg, 0.15 mmol) in acetonitrile (2 ml) was added via syringe under argon. The resulting solution was vigorously stirred in a closed vessel over 72 h at 50 °C. The reaction mixture was distilled with distilled water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4. Filtration and evaporation of the solvent provided the crude product, which was purified by column chromatography (petroleum ether and ethyl acetate), and removing the solvent in vacuo afforded benzoin (10 mg, 31%).

Reduction of Imines 11–13

A solution of imines **11–13** (0.15 mmol) in DCM (2 ml) was treated with the Hantzsch ester (HEH) (76 mg, 0.30 mmol) and a catalytic amount **8b** (8 mg, 0.015 mmol), and the mixture was stirred in a closed vessel 120 h at 60 °C under Ar.

Crystallographic Data

Crystallographic data (excluding structure factors) for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 736779. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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