Synthesis and Structure of Highly Enantio- and Diastereoenriched 1-Aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-ones Derived from Acyl-Substituted *S*-Benzyl Thiocarbamates

Oliver Stratmann, Dieter Hoppe*, and **Roland Fröhlich** [1])

Münster, Westfälische Wilhelms-Universität, Organisch-Chemisches Institut

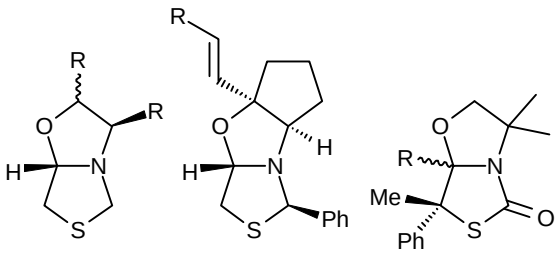
Received July 28th, 2000

Dedicated to Prof. Dr. H. Kunz on the Occasion of his 60th Birthday

Keywords: Asymmetric synthesis, Cyclizations, Nitrogen heterocycles, Sulfur heterocycles, Diastereoselective cyclizations

Abstract. A convenient method for the synthesis of the title compounds **4a**,**b**, **3a**,**b** *via* an intramolecular condensation of thiourethanes, derived from the acylation of enantioenriched α-thio benzyllithium compounds, is reported. The structure of one of the major diastereomers was elucidated by a single-crystal X-ray analysis and compared to semiempirical calculations.

Only few synthesis have been reported for the 1-aza-4-oxa-7-thiobicyclo[3.3.0]octane system, such as for **1** [1] and **2** [2]. These heterocycles constitute an interesting type of amino acetal:



1 R = 2-pyridyl; **2** R = Me, Ph; **3/4** R = Me, Et

During our studies on acylation reactions of the highly enantioenriched, configurationally stable *S*-lithiobenzyl thiocarbamate **6**, [3] we unintentionally noticed a surprisingly facile method for the formation of the corresponding 8-oxo derivatives **3** and **4** (Scheme 1).

The ketones (*R*)-**7** are stereospecifically formed from the (*S*)-lithio derivative (*S*)-**6** with complete stereoinversion on reaction with acid chlorides. When these were treated with small amounts of acidic catalysts under the usual conditions of deblocking, [3] the bicyclic compounds **3**/**4** were obtained instead of the expected *N*-(β-hydroxyalkyl)thiourethanes **8**. Besides the major diastereomers **3a** and **3b**, small amounts of a second diastereomer (**4a** and **4b**, respectively) were detected. The major diastereomer of the methyl-substituted derivative **3a** formed suitable single crystals for an X-ray crystal structure analysis, which confirms its (5*R*,6*R*)-configuration [4] (Figure 1).

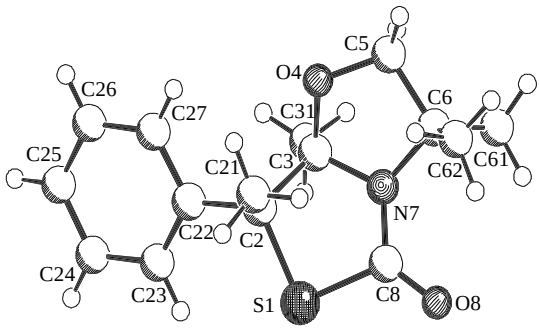
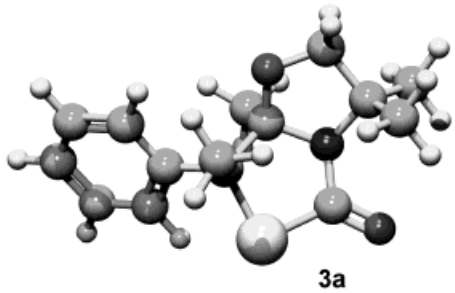
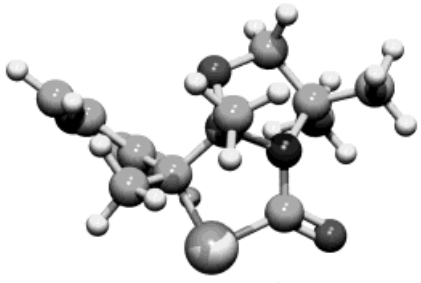


Fig. 1 X-ray crystal structure of **3a** [4]



3a



4a

Fig. 2 PM3-calculated structures for **3a** ($\Delta_f H$ = – 47.33 kcal·mol^{-1}) and **4a** ($\Delta_f H$ = – 45.88 kcal·mol^{-1})

[1]) X-ray crystal structure analysis

  1436-9966/99/3410X-828 $ 17.50 + .50/0

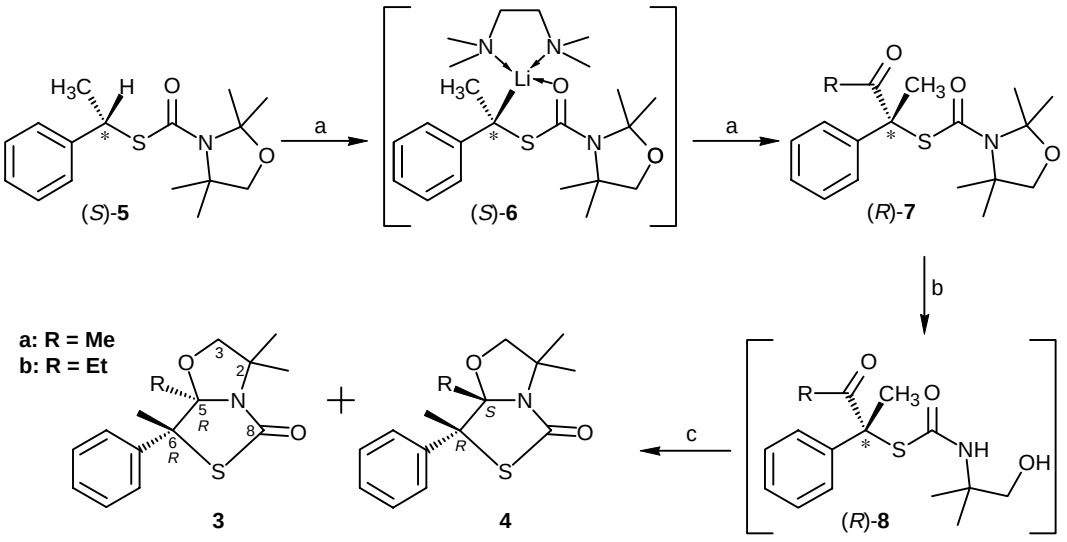
The observed diastereomeric ratios of 88:12 to 94:6, according to $\Delta\Delta G$ = 1.2 to 1.6 kcal·mol^{-1}, are in good agreement with the difference of 1.4 kcal·mol^{-1}, estimated by semi-empirical calculations [5]. The structures of **3a** and **4a**, which are the calculated energy minima, are given in Figure 2.

The tendency for the formation of these heterocycles **3**/**4** and their stability is high. Even in the presence of an excess of 1,2-ethanedithiol or 1,3-propanedithiol and boron trifluoride etherate, the bicyclic compounds **3a** and **3b** are formed with high yields.

Scheme 1 shows the complete reaction path including the *β*-hydroxy thiourethane **8**, which is supposed to be an intermediate of the cyclization process. We applied the acidic cyclization conditions to the independently synthesized [3] ethyl substituted derivative **8b**. This open-chain compound directly fuses to the bicycle **3b**/**4b** and therefore gives an additional indication for the proposed reaction path (Scheme 1).

Organisch-Chemischen Institutes der Universität Münster performed the elementary analyses on a Heraeus CHN–O-Rapid Elementaranalysator. All yields are given referring to neat products, purified by flash column chromatography [6] on silica gel (Merck, 60–200 mesh). Solvents and reagents were distilled and, if necessary, dried prior to use. Et_2O and CH_2Cl_2 were freshly distilled from Na/benzophenone and CaH_2, respectively. Isomer ratios of diastereomeric mixtures were derived from suitable ^{1}H NMR or GC integrals (Hewlett Packard HP 5890 II chromatograph with a 25 m HP 1 column or Hewlett Packard HP 6890 II chromatograph with a 25 m HP 1701 column). Values belonging to the minor diastereomer are given in curled brackets {}. All numbers in the spectroscopic data follow Scheme 1.

The ketone (**7a)** and the *β*-hydroxy thiourethane (**8b)** were synthesized as described in ref. [3].



Scheme 1 Preparation of the Title Compounds **3** and **4** a) see ref. [3]; b) 1,3-propanedithiol, Amberlyst 15, CH_2Cl_2, 8 d at *r.t.*, 99%; c) $Et_2O{\cdot}BF_3$, Et_2O, 5 d at *r.t.*, 87%.

Generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Experimental

General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 instrument at 300 MHz and 75.5 MHz, respectively. Chemical shifts are reported in ppm in relation to Me_4Si as internal standard. IR spectra were registered on a Perkin–Elmer 298 spectrometer; only the strongest bands are given. Optical rotations were obtained with a Perkin–Elmer 241 polarimeter and are specified in the unit degree·mL·dm^{-1}·g^{-1}. Melting points were measured on a Mettler FP 61 apparatus and are uncorrected. The Mikroanalytische Abteilung des

*(5*R,*6*R*)- and (5*S,*6*R*)-2,2,5,6-Tetramethyl-6-phenyl-1-aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-one* (**3a** and **4a**) [7]

The ketone (*R*)-**7a** (125 mg, 0.37 mmol, *er* > 99:1) and 1,3-propanedithiol (0.10 mL, 0.11 g, 1.0 mmol) were diluted in the suspension of the cationic ion exchanger Amberlyst 15 (34 mg) in anhydrous CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 8 d at 19 °C and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:4) and afforded **3a**/**4a** (102 mg, 0.37 mmol) as a colourless solid with 99% yield. The diastereomeric ratio of 88:12 was determined *via* GC (HP 1 and HP 1701).

***3a**/{**4a**}*

$[\alpha]_D^{20}$ = –53.1 (*c* = 1.06 in CH_2Cl_2, *dr* = 88:12, *er* ≥ 99:1 at C-6 in the starting material); R_F = 0.58 (E/P, 1:1); R_F = 0.39 (E/P, 1:2); R_F = 0.28 (E/P, 1:4); t_R = 18.4 min {17.7 min}; Δt_R =

0.72 min (HP 1); t_R = 23.7 min {22.6 min}; Δt_R = 1.12 min (HP 1701); *m.p.* 94–96 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.34 {1.31} (s, 3H, 5-CH_3); 1.50, 1.65 {1.59, 1.83} (s, 6H, 2-CH_3); 1.94 {1.89} (s, 3H, 6-CH_3); 4.21 (d, 1H, 3-H_a); 4.24 (d, 1H, 3-H_b); 7.26–7.35 (m, 5H, Ph-H); $^2J_{3Ha,\ 3Hb}$ = 14.7 Hz. – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 21.7, 23.9, 26.6, 29.7 {22.3, 22.9, 23.1, 30.1} (q, 6-CH_3, 5-CH_3, 2-CH_3); 59.0 {60.4} (s, C-6); 66.6 (s, C-2); 84.1 {82.0} (t, C-3); 104.2 {104.2} (s, C-5); 127.4, 128.9 {127.4, 129.3} (d, Ph: *o*-C, *m*-C); 128.0 {127.9} (d, Ph: *p*-C); 140.1 (s, Ph: *i*-C); 163.7 (s, C-8). – GC-MS (CI, NH_3): *m/z* (%) = 295 (82 {82}, $[M+NH_4]^{\oplus}$); 278 (100 {100}, $[M+H]^{\oplus}$); 277 (10 {10}, $M^{\oplus}$); 136 (6 {6}, $[C_8H_8S]^{\oplus}$). – GC-MS (EI, 70 eV): *m/z* (%) = 277 (100 {56}, $M^{\oplus}$); 202 (0 {5}, $[M–CH_3–COS]^{\oplus}$); 141 (22 {22}, $[Cby\text{-}CH_3]^{\oplus}$); 136 (94 {100}, $[C_8H_8S]^{\oplus}$); 121 (36 {62}, $[C_8H_8S–CH_3]^{\oplus}$); 114 (34 {42}, $[Cby\text{-}CH_3–C_2H_3]^{\oplus}$); 113 (18 {32}, $[Cby\text{-}CH_3–CO]^{\oplus}$); 98 (34 {62}, $[C_5H_8NO]^{\oplus}$ = $[Cby\text{-}C_3H_6O]^{\oplus}$). – IR (KBr): $\tilde{\nu}$/cm^{-1} = 1690 (C=O), 1680 (C=O).

$C_{15}H_{19}NO_2S$ (277.39) Calcd.: C 64.95 H 6.90 N 5.05
Found: C 64.94 H 6.88 N 5.10.

Stirring of *rac*-**7a** for 17 d at 20 °C yielded **3a**/**4a** with 85% yield and a diastereomeric ratio of 91:9 (*m.p.*: 87–89 °C).

*(5*R*,6*R*)- and (5*S*,6*R*)-5-Ethyl-2,2,6-trimethyl-6-phenyl-1-aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-one* (**3b** and **4b**)

Boron trifluoride etherate (0.10 mL, 0.11 g, 0.78 mmol) was injected to a solution of the β-hydroxy thiourethane (*R*)-**8b** (66 mg, 0.21 mmol, *er* > 98:2) in anhydrous Et_2O (2.0 mL). At 21 °C the reaction mixture was stirred for 5 d and poured into a mixture of Et_2O (5 mL) and NaOH (2 M, 5 mL). The organic layer was separated and the aqueous solution extracted with Et_2O (3*10 mL). The combined organic layers were dried over solid Mg_2SO_4. Evaporation of the solvent and flash chromatography of the crude product on silica gel (Et_2O/hexanes, 1:1) yielded the colourless solid **3b**/**{4b}** (54 mg, 0.19 mmol, 87%). The diastereomeric ratio **3b**:**4b** = 90:10 was determined by GC (HP 1). The enantiomeric ratio of (*R*):(*S*) > 98:2 concerning C-6 results from the starting material (*R*)-**7a**.

3b/{4b}

$[\alpha]_D^{21}$ = –67.7 (*c* = 0.24 in CH_2Cl_2, *dr* = 90:10, *er* > 98:2 at C-6 in the starting material); R_F = 0.66 (E/P, 1:1); t_R = 19.1 min {18.6 min}; Δt_R = 0.51 min (HP 1). – ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 0.66 (dd, 3H, 5-CH_2–C$\underline{H}_3$); 1.50, 1.67 (s, 6H, 2-CH_3); 1.74–1.94 (m, 2H, 5-C$\underline{H}_2$–CH_3); 1.96 (s, 3H, 6-CH_3); 4.17 (d, 1H, 3-H_a); 4.25 (d, 1H, 3-H_b); 7.14–7.41 (m, 5H, Ph-H); $^3J_{5\text{-}CHa\text{-}C\underline{H}3,\ 5\text{-}C\underline{H}a\text{-}CH3}$ = 7.4 Hz; $^3J_{5\text{-}CHb\text{-}C\underline{H}3,\ 5\text{-}C\underline{H}b\text{-}CH3}$ = 7.7 Hz; $^2J_{3\text{-}Ha,\ 3\text{-}Hb}$ = 8.7 Hz. – ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 9.4 {8.8} (q, 5-CH_2–C$\underline{H}_3$); 26.2, 26.3 {22.5, 22.8} (q, 2-CH_3); 28.7 {34.0} (t, 5-C$\underline{H}_2$–CH_3); 30.4 {32.2} (q, 6-CH_3); 58.6 {59.4} (s, C-6); 65.9 {66.1} (s, C-2); 84.0 {81.9} (t, C-3); 105.6 (s, C-5); 127.3, 128.3 {127.0, 128.7} (d, Ph: *o*-C, *m*-C); 127.5 {127.7} (d, Ph: *p*-C); 139.6 (s, Ph: *i*-C); 164.7 (s, C-8). – IR (film): $\tilde{\nu}$/cm^{-1} = 1695 (C=O), 1665 (C=O). – GC-MS (EI, 70 eV): *m/z* (%) = 291 (52 {24}, $M^{\oplus}$); 262 (4 {2}, $[M–C_2H_5]^{\oplus}$); 202 (20 {8}, $[M–C_2H_5–COS]^{\oplus}$); 155 (24 {20}, $[M–C_8H_8S]^{\oplus}$); 136 (100 {100}, $[C_8H_8S]^{\oplus}$); 127 (44 {32}, $[M–C_8H_8SCO]^{\oplus}$); 121 (54 {48}, $[C_8H_8S–CH_3]^{\oplus}$); 112 (70 {76}, $[M–C_8H_8SCO–CH_3]^{\oplus}$); 103 (20 {22}, $[C_8H_7]^{\oplus}$); 77 (10 {16}, $[C_6H_5]^{\oplus}$); 56 (12 {21}, $[C_4H_8]^{\oplus}$). – MS (EI, 70 eV): *m/z* (%) = 291 (52, $M^{\oplus}$); 262 (4, $[M–C_2H_5]^{\oplus}$); 202 (15, $[M–C_2H_5–COS]^{\oplus}$; 155 (23, $[M–C_8H_8S]^{\oplus}$); 136 (100, $[C_8H_8S]^{\oplus}$); 127 (54, $[M–C_8H_8SCO]^{\oplus}$); 121 (78, $[C_8H_8S–CH_3]^{\oplus}$); 112 (92, $[M–C_8H_8SCO–CH_3]^{\oplus}$); 103 (36, $[C_8H_7]^{\oplus}$); 77 (24, $[C_6H_5]^{\oplus}$); 56 (36, $[C_4H_8]^{\oplus}$). HR-MS (EI, 70 eV) calcd. for $C_{16}H_{21}NO_2S$ [$M^{\oplus}$] 291.1293, found 291.1294.

References

[1] M. F. Aly, H. Ardill, R. Grigg, S. Leong-Ling, S. Rajviroongit, S. Surendrakumar, Tetrahedron Lett. **1987**, *28*, 6077

[2] S. Kanemasa, K. Doi, E. Wada, Bull. Chem. Soc. Jpn. **1990**, *63*, 2866

[3] O. Stratmann, B. Kaiser, R. Fröhlich, O. Meyer, D. Hoppe, Chem. Eur. J. **2000**, *6*, in print

[4] The single-crystal for the X-ray crystal structure analysis was obtained by crystallization from diethyl ether at –30 °C and separation of the mother liquor. X-ray crystal structure analysis of **3a**: formula $C_{15}H_{19}NO_2S$, M = 277.37, colourless crystal 0.40 × 0.30 × 0.10 mm, a = 11.114(1), b = 11.269(1), c = 11.820(1) Å, β = 102.44(1)°, V = 1445.6(2) Å^3, ρ_{calc} = 1.274 g cm^{-3}, μ = 2.22 cm^{-1}, empirical absorption correction *via* SORTAV (0.917 ≤ T ≤ 0.978), Z = 4, monoclinic, space group $P2_1$ (No. 4), λ = 0.71073 Å, T = 198 K, ω and phi scans, 10527 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.65 Å^{-1}, 5831 independent (R_{int} = 0.043) and 5526 observed reflections [$I \geq 2\ \sigma(I)$], 351 refined parameters, R = 0.035, wR^2 = 0.082, max. residual electron density 0.28 (–0.18) e Å^{-3}, Flack parameter –0.03(5), two almost identical independent molecules in the asymmetric unit, hydrogens calculated and refined as riding atoms. Data set was collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, Methods in Enzymology, **1997**, *276*, 307), absorption correction SORTAV (R. H. Blessing, Acta Cryst. **1995**, *A51*, 33; R. H. Blessing, J. Appl. Cryst. **1997**, *30*, 421), structure solution SHELXS-97 (G. M. Sheldrick, Acta Cryst. **1990**, *A46*, 467), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg 1997). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 146736. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

[5] The program MOPAC (J. J. P. Stewart, J. Comp. Aided Molecular Design, Special Issue **1990**, *4*, Nr. 1) was used with PM3 parameters (J. J. P. Stewart, J. Comp. Chem. **1989**, *10*, 209).

[6] W. C. Still, M. Kahn, A. Mitra J. Org. Chem. **1978**, *43*, 2923

[7] Different conditions for preparing **3a**/**{4a}**: A) Stirring of the ketone (*R*)-**7a** (105 mg, 0.31 mmol, *er* > 98:2) in anhydrous CH_2Cl_2 (3.0 mL) 1,2-ethanedithiol (0.42 mL, 0.47 g, 5.0 mmol) and boron trifluoride etherate (0.10 mL, 0.11 g, 0.78 mmol) for 10 d resulted in **3a**/**4a** (52 mg, 0.19 mmol, 61 %) with *m.p.* 94–96 °C and $[\alpha]_D^{20}$ = –57.2 (*c* = 0.75 in CH_2Cl_2, *dr* = 94:6, *er* ≥ 98:2 at C-6 in the starting material). B) Without exclosure of moisture the ketone *rac*-**7a** (133 mg,

0.40 mmol), Amberlyst 15 (40 mg) and CH_3OH (0.5 mL) were heated for 34 h to 100 °C in a pressure-proof vessel. After the solvent had been evaporated *in vacuo*, the residue was purified by flash chromatography **3a**/**4a** (89 mg, 0.32 mmol) were isolated with 81% yield and a diastereomeric ratio of 89:11 (GC: HP 1; *m.p.* 89–90 °C).

Address for correspondence:
Prof. Dr. D. Hoppe
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut der Universität
Corrensstr. 40
D-48149 Münster
Fax: Internat. code (0)251-8339772
e-Mail: dhoppe@uni-muenster.de