Synthesis of Chiral 3,4,5,6-Tetrahydro-1,4-thiazin-2-ones (Thiamorpholin-2-ones) – Novel Heterocycles Possessing Enhanced Carbonyl Electrophilicity over their Oxygen Counterparts

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Abstract: We report herein the first synthesis of chiral derivatives possessing the 1,4-thiazinone core. As predicted, the thiolactone is more susceptible to nucleophilic attack than the equivalent lactone system.

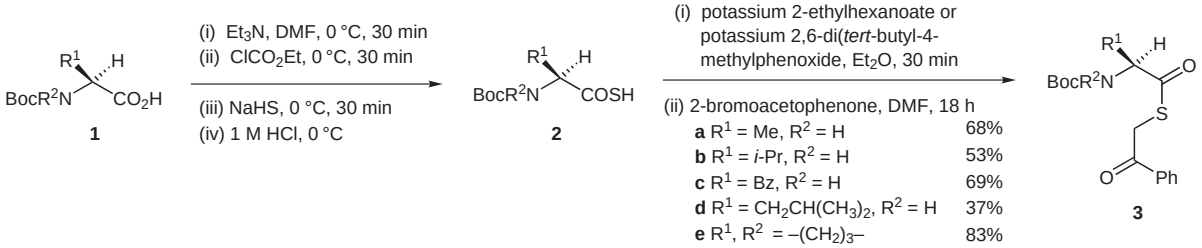
Key words: chiral, 1,4-thiazinone, thiamorpholinone

We have published extensively in the area of chirality relay using chiral morpholinones as substrates for azomethine ylide generation and trapping,[1] observing on occasion nucleophilic ring opening of the lactone.[2] Wishing to utilize this side reactivity in another application, we decided to synthesize thiamorpholinone analogues in the expectation that nucleophilic attack on the thiolactone of these templates (for which no general synthetic pathway exists[3]) should occur more readily and under milder conditions.

We proposed that the desired 3,5-disubstituted thiamorpholinones could be constructed by conversion of Boc-protected amino acids to their corresponding potassium thionate salts according to literature precedent;[4] then adapting Caplar and Sunjic's method for morpholinone synthesis.[5] However, we recognized that we could run into difficulties at the final hydrogenation step, as the presence of sulfur in the substrates was likely to poison any transition-metal catalyst and it was not predictable whether we could achieve efficient diastereocontrol with alternative reducing agents if catalyzed hydrogenation proved impossible.

The triethylamine salts of five representative Boc-protected L-amino acids **1a**–**e** were C-terminus-activated with ethyl chloroformate at 0 °C and then reacted with sodium hydrosulfide hydrate to form a dark green solution within 30 minutes which was acidified by addition of 1 M hydrogen chloride to pH 2. The thioacids **2a**–**d** thus obtained were converted into the corresponding potassium salts using potassium 2-ethyl hexanoate (KEH) in diethyl ether following a previously described protocol.[4] In the case of thioproline derivative **2e**, the potassium salt was generated using potassium 2,6-di(*tert*-butyl)-4-methylphenoxide. These salts were then reacted with 2-bromoacetophenone to generate the thioesters **3a**–**e** in yields of (68%, 53%, 69%, 37% and 83% yields, respectively, over the whole sequence (Scheme 1).

After removing the Boc group from **3a** with 20% trifluoroacetic acid in dichloromethane, the cyclization was initially attempted using pH 5 acetate buffer, conditions successful in the morpholinone series, but after 18 hours only decomposed materials were recovered from the aqueous phase; presumably due to hydrolysis of the thioester. However, when the deprotected amine was treated with anhydrous potassium carbonate in dry dichloromethane, a new material was observed by TLC analysis and the reaction was found to be complete within 24 hours.[6] On work-up and purification a 59% yield of cyclized material was obtained and this was found to be a mixture of two inseparable isomers in a ratio of 2:1. The major component was shown to be the expected imine **4a** by analogy with the observations of Caplar and Sunjic and the minor one was identified as the enamine **5a** by ^{1}H NMR spectroscopic analysis. Two doublets at δ = 4.22 (J = 15.3 Hz) ppm and δ = 3.96 (J = 15.3 Hz) ppm corresponded to the methylene group in the imine **4a** and a



Scheme 1

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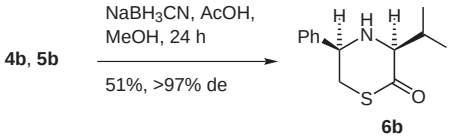
singlet at δ = 5.22 ppm corresponded to the alkene proton of the enamine.[7] Substrates **3b**–**d** behaved similarly furnishing mixtures of cyclized materials in 49%, 53% and 57% yields, respectively, with the exception that cesium carbonate proved more effective for producing the 3-isopropyl-substituted isomers **4b** and **5b** and the 3-benzyl isomers **4c** and **5c** were obtained in a 1:1 ratio (Scheme 2). In the case of **3e**, cyclization led to **5e** in an isolated crude yield of 72%, but the product proved too labile to purify completely.

With the 3,5-disubstituted dihydro-1,4-thiazin-2-ones **4** and **5** in hand, our final task was to reduce them to the desired thiamorpholinones **6**. However, using the mixture of 3-methyl-substituted substrates **4a** and **5a** our earlier fears were realized when it was found that these compounds resisted various catalytic hydrogenation conditions. Moreover, when treated with hydride donors such as sodium borohydride or sodium cyanoborohydride in methanol, only decomposition was observed. Frustratingly, a combination of aluminium and nickel chloride in aqueous THF[8] was successful on the initial attempt (albeit giving low yield and stereoselectivity) but could not be repeated despite numerous attempts and modifications of the conditions.

Although decomposition occurred under the sodium borohydride or sodium cyanoborohydride conditions, the enamine olefin proton signal in the ^{1}H NMR spectrum and the imine carbon signal in the ^{13}C NMR spectrum of crude material also disappeared. From these observations, we proposed that the imine and the enamine had been reduced, but the resultant 3-methylthiamorpholinone **6a** was subsequently destroyed. Believing this might be due to lability of the thiolactone, we turned our attention to the 3-isopropyldidehydrothiamorpholinones **4b** and **5b** when the reduced product might be more resistant to subsequent decomposition as a result of the Thorpe–Ingold effect favouring ring closure.

Based on previous observations, sodium cyanoborohydride in methanol was chosen as the reducing reagent to attempt the transformation of the mixture of **4b** and **5b**. It was found that the mixture of starting materials was slowly converted into a single less polar compound and the addition of a few drops of acetic acid greatly accelerated this process. The new compound was isolated in 51% purified yield and identified as the desired *syn*-3(*S*)-isopropyl-5(*R*)-phenylthiamorpholinone (**6b**) by ^{1}H NMR analysis (Scheme 3); three double doublets at δ = 4.23 (*J* = 10.9 Hz, *J*′ = 2.9 Hz) ppm, δ = 3.46 (*J* = 11.6 Hz, *J*′ = 10.9 Hz,) δ = 3.07 (*J* = 11.6 Hz, *J*′ = 2.9 Hz) corresponding to the ABX system at C-5 and C-6 being diagnostic; the relative stereochemistry being concluded initially from NOE difference experiments. Further evidence for reduction was obtained from the mass spectrum in which the mass ion at 236 [MH$^+$] could be observed.



Scheme 3

Furthermore, from inspection of the ^{1}H NMR spectrum of the crude material it was clear that this reduction was highly diastereoselective (>97% de). The conclusions based upon spectroscopic analysis were upheld by X-ray crystallographic analysis[9] which showed that the thiamorpholinone ring adopts a flattened chair conformation with the *syn*-3,5-substituents in equatorial environments, in direct analogy with the analogous morpholinone systems previously studied (Figure 1).[10] From this we conclude that the hydride attacks the intermediate iminium species from the opposite face to the isopropyl group.

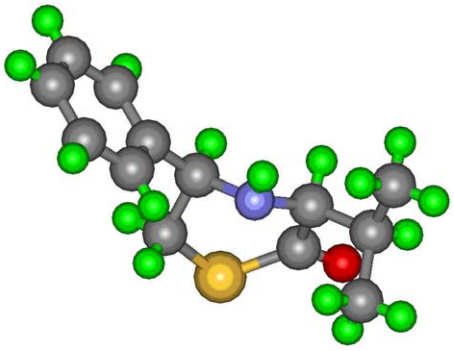
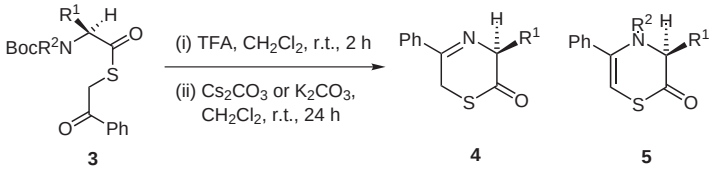


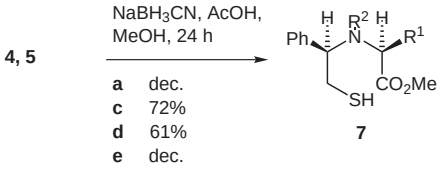
Figure 1 Crystal structure of **6b**

However, when we turned our attention to the analogues **4c**,**d** and **5c**,**d**, not only did stereoselective reduction occur but the resultant thiolactone underwent nucleophilic attack by the solvent giving rise to the open-chain methyl esters **7c**,**d**; whereas the alanine and proline derived materials **4a**, **5a**,**e** decomposed, providing clear evidence of the greater propensity of the thiolactone to undergo nucleophilic attack compared to the morpholinone analogues which are stable towards these conditions (Scheme 4).



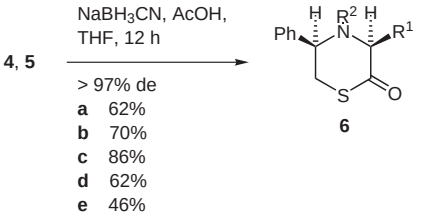
	yield	ratio 4 : 5
a	59%	1 : 2
b	49%	1 : 2
c	53%	1 : 1
d	57%	1 : 2
e	72%	0 : 1

Scheme 2



Scheme 4

However, the simple expedient of substituting THF for the methanol solvent permitted isolation of the desired 3,5-disubstituted thiamorpholinones **6a**–**e** in 62%, 70%, 86%, 62% and 46% yields, respectively, with excellent diastereoselectivity (>97% from examination of crude product mixtures) in all cases (Scheme 5).



Scheme 5

In conclusion, we have developed an efficient synthetic route to novel chiral thiamorpholinones, which demonstrate increased propensity towards nucleophilic ring opening compared with their morpholinone counterparts.

Acknowledgment

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References and Notes

(1) For recent communications, see: (a) Draffin, W. N.; Harwood, L. M. *Synlett* **2006**, 857. (b) Aldous, D. J.; Drew, M. G. B.; Draffin, W. N.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synthesis* **2005**, 3271. (c) Aldous, D. J.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synlett* **2001**, 1841. (d) Aldous, D. J.; Drew, M. G. B.; Hamelin, E. M.-N.; Harwood, L. M.; Jahans, A. B.; Thurairatnam, S. *Synlett* **2001**, 1836; see also references cited therein.

(2) (a) Harwood, L. M.; Robertson, S. M. *J. Chem. Soc., Chem. Commun.* **1998**, 2641. (b) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089.

(3) A few reports of thiamorpholinones embedded within β-lactam structures have appeared: (a) Costerousse, G.; Cagniant, A.; Didierlaurent, S. *Bull. Soc. Chim. Fr.* **1989**, 830. (b) Hakimelahi, G. H.; Tsay, S.-C.; Ramezani, Z.; Hwu, J. R. *Helv. Chim. Acta* **1996**, *79*, 813.

(4) Gottstein, W. J.; Babel, R. B.; Crast, L. B. *J. Med. Chem.* **794**, *8*, 1965.

(5) Caplar, V.; Lisini, A.; Kajfez, F.; Sunjic, V. *J. Org. Chem.* **1978**, *43*, 1355.

(6) **Representative Experimental Procedures.**
Cyclization of 3a to Produce 4a and 5a.
To a solution of 2-oxo-2-phenylethyl-(*S*)-*N*-Boc-thioalanate (**3a**, 3.88 g, 12 mmol) in anhyd CH_2Cl_2 (50 mL) was added TFA (12.5 mL). The resulting solution was stirred under an atmosphere of nitrogen for 2 h. The solvent and the excess of TFA were removed in vacuo and the residue was dissolved in anhyd CH_2Cl_2 (50 mL) to which K_2CO_3 (8.28 g, 60 mmol, 5.0 equiv) was added. The resulting mixture was stirred under an atmosphere of nitrogen for 24 h. Filtration through a short pad of Celite® and removal of solvent from the filtrate in vacuo gave the crude material which was purified by flash column chromatography on silica, eluting with light PE and Et_2O (4:1) to furnish the inseparable mixture of title products as a yellow oil (1.44 g, 59%).
Reduction of 4a and 5a to Produce 6a.
To a solution of (*S*)-3-methyl-5-phenyl-4,5-didehydro-1,4-thiazin-2-one (**4a**) and (*S*)-3-methyl-5-phenyl-5,6-didehydro-1,4-thiazin-2-one (**5a**, 100 mg, 0.49 mmol) in anhyd THF (5 mL) was added sodium cyanoborohydride (62 mg, 0.97 mmol 2.0 equiv) and AcOH (ca. 5 drops). The resulting solution was stirred under an atmosphere of nitrogen for 12 h. The solvent was removed in vacuo to give the crude material which was purified by flash column chromatography on silica, eluting with light PE and Et_2O (8:1, then 4:1) to furnish the title product as a pale yellow oil (63 mg, 62%).
Reduction and Thiolactone Cleavage to Produce 7d.
To a solution of (*S*)-3-(2-methylpropyl)-5-phenyl-4,5-didehydro-1,4-thiazin-2-one (**4d**) and (*S*)-3-(2-methylpropyl)-5-phenyl-5,6-didehydro-1,4-thiazin-2-one (**5d**, 92 mg, 0.38 mmol) in anhyd MeOH (8 mL) was added sodium cyanoborohydride (70 mg, 1.12 mmol, 3.0 equiv) and AcOH (ca. 5 drops). The resulting solution was stirred under an atmosphere of nitrogen for 24 h. The solvent was removed in vacuo to give the crude material which was purified by flash column chromatography on silica, eluting with light PE and Et_2O (4:1) to furnish the title product as a pale yellow oil (56 mg, 61%).

(7) **Representative Analytical Data.**
Compounds **4a** and **5a** (mixture): IR (film): ν_{max} = 3391 (N–H), 2983 (C–H), 1683 (C=O, thiolactone) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 7.74–7.27 (5 H, m, Ph), 5.22 (0.35 H, s, PhC=CH), 4.22 (0.65 H, d, *J* = 15.3 Hz, CH_2S), 4.02–3.97 (0.65 H, m, CH_3CH), 3.96 (0.65 H, d, *J* = 15.3 Hz, CH_2S), 3.66–3.61 (0.35 H, m, CH_3CH), 1.59 (1.95 H, d, *J* = 6.3 Hz, $CHCH_3$), 1.32 (1.05 H, d, *J* = 7.3 Hz, $CHCH_3$). MS (CI): *m/z* (%) = 205 (44) [M^+], 181 (66), 162 (100). HRMS: *m/z* calcd for $C_{11}H_{11}NOS$: 205.0561; found: 205.0562.
Compound **6a**: IR (film): ν_{max} = 3319 (N–H), 2929 (C–H), 1668 (C=O, thiolactone) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.45–7.32 (5 H, m, Ph), 4.30 (1 H, dd, *J* = 10.82 Hz, *J*′ = 3.31 Hz, PhCH), 3.86 (1 H, q, *J* = 6.67 Hz, $CHCH_3$), 3.55 (1 H, dd, *J* = 11.69 Hz, *J*′ = 10.82 Hz, CH_2S), 3.13 (1 H, dd, *J* = 11.69 Hz, *J*′ = 3.31 Hz, 1 × CH_2S), 1.89 (1 H, br, NH), 1.40 (1 H, d, *J* = 6.67 Hz, $CHCH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.6, 142.3, 129.4, 128.8, 126.8, 65.2, 60.1, 38.8, 18.2. MS (CI): *m/z* (%) = 208 (51) [MH^+], 131 (46), 121 (100). HRMS: *m/z* calcd for $C_{11}H_{14}NOS$: 208.0796; found: 208.0788. $[\alpha]_{436}^{20}$ –1.0 (*c* 0.70 $CHCl_3$), $[\alpha]_D^{20}$ 0.0 (*c* 0.70 $CHCl_3$).
Compound **7d**: IR (film): ν_{max} = 3308 (N–H), 2956 (C–H), 1734 (C=O, ester) cm^{-1}. ^{1}HNMR (250 MHz, $CDCl_3$): δ = 7.29–7.17 (5 H, m, Ph), 3.63 (3 H, s, CH_3O), 3.47 (1 H, dd, *J* = 8.7 Hz, *J*′ = 4.8 Hz, PhCH), 2.95 [1 H, dd, *J* = 8.9 Hz, *J*′ = 5.5 Hz, $(CH_3)_2CHCH_2CH$], 2.76 (1 H, dd, *J* = 13.3 Hz, *J*′ = 4.6 Hz, CH_2S), 2.51 (1 H, m, CH_2S), 1.78–1.72 [1 H, m, $(CH_3)_2CHCH_2$], 1.41–1.26 [2 H, m, $(CH_3)_2CHCH_2$], 0.79 [3 H, d, *J* = 6.6 Hz, 3 × $(CH_3)_2CH$], 0.62 [3 H, d, *J* = 6.6 Hz, 3 × $(CH_3)_2CH$]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 175.5,

140.8, 127.5, 126.8, 126.5, 62.6, 55.9, 50.6, 42.2, 31.8, 23.6, 22.1, 20.7. MS (CI): *m/z* (%) = 282 (55) [M^+], 234 (100), 174 (16). HRMS: *m/z* calcd for $C_{15}H_{24}NO_2S$: 282.1528; found: 282.1526. $[\alpha]_D^{20}$ –4.6 (*c* 0.77 $CHCl_3$).

(8) Bhabani, K.; Barua, N. C. *Tetrahedron* **1991**, *47*, 8587.

(9) **X-ray Crystal Data of 6b.**
$C_{13}H_{17}NOS$, *M* = 235.34, triclinic, space group *P*1, *Z* = 8, *a* =& nbsp;9.7241 (8), *b* = 13.4169 (12), *c* = 19.8594 (17), *V* = 2437 Å^3, *d* = 1.283 g cm^3, 12166 independent reflections were collected with MoK_α radiation on a MARresearch Image Plate system. Data analysis was carried out with the XDS program,[11] the structure was solved by direct methods using Shelx86[12] and refined on F2 using Shelx[13] to *R*1 = 0.1039, *wR*2 = 0.1641. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Database Service. Please quote reference number CCDC 617867.

(10) For example, see: (a) Drew, M. G. B.; Harwood, L. M.; Price, D. W.; Park, G. *Tetrahedron Lett.* **2000**, 5077. (b) Drew, M. G. B.; Harwood, L. M.; Park, G.; Price, D. W.; Tyler, S. N. G.; Park, C. R.; Gho, S. G. *Tetrahedron* **2001**, *57*, 5641.

(11) Kabsch, W. *J. Appl. Cryst.* **1988**, *21*, 916.

(12) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Fundam. Crystallogr.* **1990**, *46*, 467.

(13) Sheldrick, G. M. *Program for Crystal Structure Refinement*; University of Göttingen: Germany, **1993**.