A Novel Method for the Stereoselective Synthesis of Thiiran-2-ylmethyl Alkylcarbamates

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Abstract: A highly efficient stereoselective conversion of *N*-alkyl-5-(acyloxymethyl)-1,3-oxathiolane-2-imines into thiiran-2-ylmethyl alkylcarbamates is described. The reaction is catalyzed by sodium methoxide and proceeds under mild conditions at room temperature in methanol.

Key words: thiiranes, imines, esters, tandem reaction, stereoselectivity

Thiiranes are used in organic synthesis, polymer chemistry and for preparing medicines, insecticides and herbicides.[1] For instance, thiiran-2-ylmethyl derivatives are employed as inhibitors of human matrix metalloproteinases[1] and of topoisomerases.[2] The reaction of thiiranes with ammonia and amines is utilized for preparing taurine derivatives,[3] a class of naturally occurring amino sulfonic acids. To date, the most efficient method for thiirane synthesis involves the conversion of oxiranes into the corresponding thiiranes using various reagents such as thiourea and thiocyanic acid salts,[4] phosphine sulfide[5] or *N*,*N*-dimethylthioformamide.[6] Since non-racemic thiiranes are required for the synthesis of enzyme inhibitors[1,2] and chelating chiral ligands,[7] additional steps for separating racemic mixtures must be performed. To improve the existing methods for thiirane synthesis, several groups have investigated approaches for the production of enantiomerically pure thiiranes. One of these studies involved reactions of enantiomerically enriched oxiranes with thiourea in methanol.[8] An alternative method used β-hydroxythiocyanates which are known intermediates for the synthesis of thiiranes. Enantiomerically enriched 1-substituted 3-thiocyanatopropan-2-ols have been prepared by lipase-catalyzed hydrolysis of the corresponding racemic acetates[9] and by asymmetric reduction of α-thiocyanatoketones with Baker's yeast.[10]

Taking advantage of the faster alkylation of the thiocyanato group compared to the intramolecular cyclization of β-hydroxythiocyanates, we previously developed a convenient method for the synthesis of *N*-alkyl-1,3-oxathiolan-2-imines of type **1**.[11] These compounds proved to be useful substrates for the synthesis of alkoxy ureas,[11c] 1,3-oxathioles,[12] 1,3-dithiolanes,[13] and biologically active compounds such as insecticides, herbicides and anti-cancer agents.[14]

Herein, we report a novel method for the synthesis of thiiranes **2** from *N*-alkyl-5-(acyloxymethyl)-1,3-oxathiolan-2-imines **1**. We intended to take advantage of the properties of imines **1**, which contain both imino and ester groups, to enable their simultaneous or preferential hydrolysis. Our initial attempts to hydrolyze preferentially the ester group in aqueous methanolic sodium hydroxide yielded predominantly polymeric products. To avoid polymerization and to improve the yield of the target products, we explored the effectiveness of methanolysis in the presence of a catalyst. We found that sodium methoxide catalyzed effectively the formation of thiiran-2-ylmethyl carbamates **2a**,**b** (Scheme 1). Thin-layer chromatographic monitoring showed that the reaction was complete within ten minutes at room temperature, with no polymeric products being detected. In the case of the 5-(benzoyloxymethyl) derivatives **1a** and **1b**, the corresponding products were isolated in high yields by means of column chromatography. The products formed from the 5-(acetyloxymethyl) derivatives **1c** and **1d** did not require chromatographic purification. It was proposed that the reaction of 1,3-oxathiolane-2-imines with anionic nucleophiles should lead to the formation of *S*-(oxiran-2-ylmethyl) carbamothioates.[13,15] Interestingly, under our conditions, the products of these reactions were thiiran-2-ylmethyl carbamates **2a**,**b**.

In order to investigate the mechanism of this reaction we synthesized (5*R*)-*N*-(1-adamantyl)-5-(benzoyloxymethyl)-1,3-oxathiolan-2-imine (**1a**) from (2*S*)-oxiran-2-ylmethyl benzoate,[16a] itself prepared by a method described elsewhere.[16] The *R*-configuration of compound **1a** was confirmed by X-ray analysis (Figure 1). Our data showed that each crystal cell contained two molecules of **1a** in different twisted conformations of the oxathiolane ring and that the imino group of each molecule had the *E*-configuration. The reaction of dextrorotatory (*R*)-**1a** yielded the levorotatory product (*S*)-**2a** whilst the dextrorotatory carbamate **2b** was prepared from the levorotatory imine **1d**. The configurations of the thiiran-2-ylmethyl derivatives **2a** and **2b** were deduced based on the fact that all known (*S*)-thiiran-2-ylmethyl esters and ethers are levorotatory.[3a,8c,9b,10] We have confirmed the configuration of (*R*)-**2b** from time-dependent density functional theory (TDDFT) calculations of specific rotations according to the corre-

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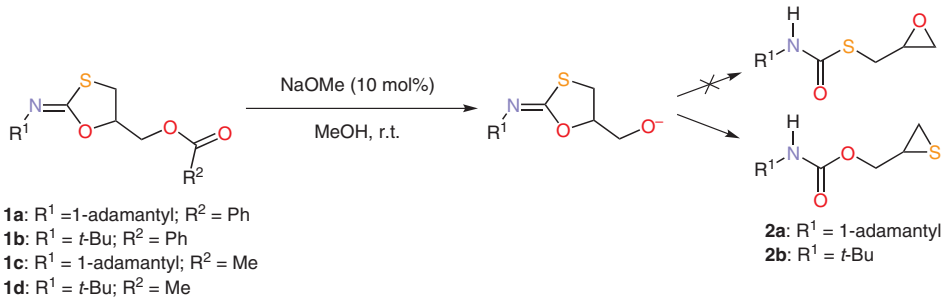


Scheme 1 Synthesis of thiiran-2-ylmethyl carbamates **2a**,**b**

sponding calculations on (*S*)-epichlorohydrin.[17] Calculations of the energies of the conformers of carbamate (*R*)-**2b** at the B3LYP/6-311+G* level of theory indicated eight stable conformers with populations of not less than 1% in dichloromethane at 298 °K. The following specific rotation calculations of these conformers at five wavelengths using the B3LYP/aug-cc-pVDZ level gave the Boltzmann averaged values. A comparison of the calculated and experimental (in parentheses, *c* 1.11, CH_2Cl_2, 20 °C) specific rotation values confirmed the (*R*)-configuration of carbamate **2b** according to the known criteria:[18] +49.4 (+31.2) at 589 nm, +57.6 (+36.5) at 546 nm, +89.4 (+53.1) at 436 nm, +101.4 (+64.3) at 405 nm, and +115.0 (+77.6) at 365 nm.

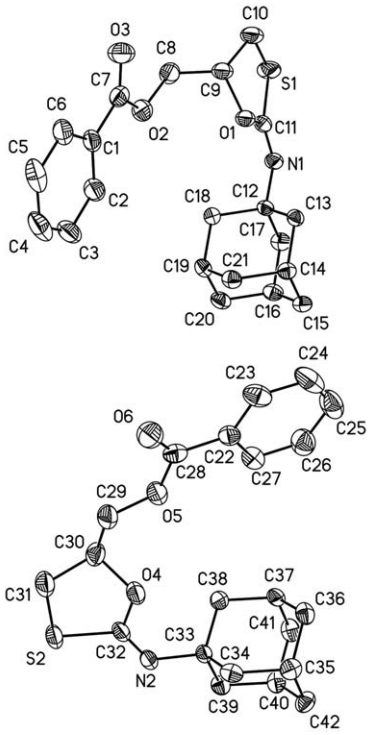
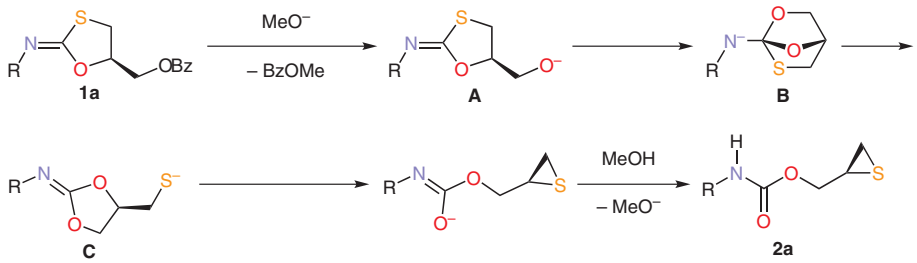


Figure 1 Crystal structure of (*R*)-*N*-(1-adamantyl)-5-(benzoyloxymethyl)-1,3-oxathiolan-2-imine (**1a**) (ORTEP view); hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): C11–N1 = 1.257, C11–S1 = 1.767, C11–O1 = 1.368, C11–S1–C10 = 91.9, C11–O1–C9 = 112.9, O1–C9–C10–S1 = 35.4, O4–C30–C31–S2 = –41.4.

These data suggest that the transformation of (5*R*)-*N*-(1-adamantyl)-5-(benzoyloxymethyl)-1,3-oxathiolan-2-imine (**1a**) into (2*S*)-thiiran-2-ylmethyl 1-adamantylcarbamate (**2a**) proceeds via several intermediates, which are shown in Scheme 2. Structures **A** and **C** could form stable products whilst the bicyclic structure **B** could exist as an intermediate or a transition state. The formation of a similar cage bicyclic intermediate or transition state could be postulated for the transformation of the azidomethyl lactone fragment of pyridooxazinones into the hydroxy lactam fragment of pyridodiazepinones via Staudinger reduction.[19] Also, a proposed mechanism for the 2,3-epoxy alcohol *O*-thiocarbamate rearrangement includes an *N*,*N*-dimethyl-1,3-oxathiolane-2-immonio intermediate which is transformed into a mixture of thiiran-2-ylmethyl dimethylcarbamate derivatives via the same bicyclic structure.[20]

In conclusion, we have described a new method for the synthesis of thiiranes via a tandem reaction. Initial alkali-catalyzed methanolysis of the ester group of the *N*-alkyl-5-(acyloxymethyl)-1,3-oxathiolane-2-imine is then followed by spontaneous intramolecular rearrangement leading to thiirane formation. The reaction is characterized by stereoselectivity, high yields and mild conditions. We believe that this reaction provides a practical alternative to existing methods available for the synthesis of both racemic and enantiomerically enriched thiiranes.



Scheme 2 Transformation of **1a** into thiirane **2a**

All commercially obtained reagents were used without further purification unless stated otherwise. All solvents were distilled prior to use. Melting points were obtained using a PTP melting point apparatus and are uncorrected. All the reactions were monitored by TLC performed on precoated silica gel plates (Merck). Compounds were made visual with I_2. IR spectra of samples prepared as KBr pellets were recorded on a Shimadzu FTIR-8500S spectrometer. NMR spectra were recorded on a Bruker AM 300 spectrometer; TMS was used as an internal standard. The number of signals in the ^{13}C NMR spectra for compounds **1a**–**d** correspond to the fact that these compounds are mixtures of *Z*/*E*-isomers[11b] in solution. Mass spectra were recorded in DEP mode on a Finnigan DSQ GC–MS. Elemental analyses were obtained using a EuroEA Elemental Analyzer. Optical rotations were measured with an Autopol V Plus polarimeter. All calculations were performed using the Gaussian program[21] with the PCM implicit solvation model. (2*R*)-Oxiran-2-ylmethyl acetate was prepared by hydrolytic kinetic resolution[22] of the corresponding racemate catalyzed by (*S*,*S*)-(salen)Co(III)OAc complex; $[\alpha]_D^{22}$ 29.6 (neat) {Lit.[23] $[\alpha]_D^{22}$ 29.9 (neat)}.

N-Alkyl-5-(acyloxymethyl)-1,3-oxathiolan-2-imines; General Procedure

NH_4SCN (0.95 g, 12 mmol) was added to a soln of the appropriate oxirane (12 mmol) in glacial AcOH (6 mL, 100 mmol) at 15 °C, and the mixture stirred for 2 h at 15 °C. Next, this mixture was added dropwise to a soln of 1-adamantanol (1.8 g, 12 mmol) in H_2SO_4 (12 mL, *d* 1.84) at 0–5 °C. In the case of *tert*-butyl derivatives **1b**,**d**, *t*-BuOH (1.4 mL, 15 mmol) was dissolved in the NH_4SCN–oxirane–AcOH mixture and the resulting soln added dropwise to H_2SO_4 (12 mL, *d* 1.84) at 0–5 °C. The mixture was poured onto ice and extracted with $CHCl_3$ (3 × 20 mL). The aq layer was neutralized with Na_2CO_3 (until pH >9), extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried (Na_2SO_4), filtered over silica gel (5 g) and the solvent removed by distillation.

(5*R*)-*N*-(1-Adamantyl)-5-(benzoyloxymethyl)-1,3-oxathiolan-2-imine (1a)

Yield: 1.92 g (43%); white needles; mp 105–107 °C (acetone); $[\alpha]_D^{20}$ +21.0 (*c* 1.25, benzene).

IR (KBr): 2908, 1720, 1662, 1261, 1056, 714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.73 (m, 6 H), 1.92–2.03 (m, 6 H), 2.10–2.20 (m, 3 H), 3.15–3.48 (m, 2 H), 4.35–4.45 (m, 2 H), 4.51–4.59 (m, 0.5 H), 4.81–4.90 (m, 0.5 H), 7.40–7.50 (m, 2 H), 7.51–7.60 (m, 1 H), 8.02–8.11 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 29.9, 31.7, 34.9, 36.5, 36.6, 41.8, 42.5, 53.3, 56.7, 64.1, 64.2, 75.2, 80.4, 128.5, 129.4, 129.9, 133.5, 153.4, 155.4, 166.2.

MS (EI, 70 eV): *m*/*z* (%) = 371 (12) $[M]^+$, 194 (91), 177 (12), 161 (25), 135 (35), 120 (30), 105 (100), 93 (17), 77 (38), 72 (60).

Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78; N, 3.77; S, 8.63. Found: C, 67.81; H, 6.77; N, 3.67; S, 8.45.

(5*R*/*S*)-*N*-*tert*-Butyl-5-(benzoyloxymethyl)-1,3-oxathiolan-2-imine (1b)

Yield: 2.64 g (70%); colorless oil.

IR (KBr): 2966, 1724, 1670, 1272, 1095 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 3.11–3.44 (m, 2 H), 4.35–4.49 (m, 2 H), 4.55–4.65 (m, 0.5 H), 4.85–4.95 (m, 0.5 H), 7.30–7.40 (m, 2 H), 7.41–7.51 (m, 1H), 7.95–7.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 29.6, 31.4, 34.2, 52.5, 55.4, 63.7, 64.8, 75.1, 80.2, 128.1, 128.2, 129.0, 129.2, 129.4, 129.5, 133.0, 133.1, 165.6.

MS (EI, 70 eV): *m*/*z* (%) = 293 (2) $[M]^+$, 195 (16), 105 (80), 84 (100), 77 (45), 73 (38), 72 (27), 57 (29).

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.38; H, 6.58; N, 4.61; S, 10.66.

(5*R*/*S*)-*N*-(1-Adamantyl)-5-(acetyloxymethyl)-1,3-oxathiolan-2-imine (1c)

Yield: 2.26 g (61%); white needles; mp 90–91 °C (acetone).

IR (KBr): 2904, 1735, 1666, 1276, 1064 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.66 (m, 6 H), 1.75–1.90 (m, 6 H), 1.92–2.08 (m, 3 H), 2.10 (s, 3 H), 3.05–3.40 (m, 2 H), 4.25–4.30 (m, 2 H), 4.42–4.52 (m, 0.5 H), 4.72–4.82 (m, 0.5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 20.6, 29.5, 29.7, 31.5, 34.5, 36.2, 36.4, 41.6, 42.4, 53.0, 56.4, 63.2, 63.4, 74.9, 80.1, 152.9, 154.8, 170.2, 170.3.

MS (EI, 70 eV): *m*/*z* (%) = 309 (10) $[M]^+$, 177 (15), 135 (36), 132 (72), 120 (47), 73 (42), 72 (100), 43 (36).

Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36. Found: C, 62.15; H, 7.40; N, 4.48; S, 10.10.

(5*S*)-*N*-*tert*-Butyl-5-(acetyloxymethyl)-1,3-oxathiolan-2-imine (1d)

Yield: 1.97 g (71%); colorless oil; $[\alpha]_D^{20}$ –15.5 (*c* 1.12, benzene).

IR (KBr): 2968, 1746, 1669, 1234, 1047 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 9 H), 1.97 (s, 3 H), 3.02–3.38 (m, 2 H), 4.12–4.28 (m, 2 H), 4.40–4.50 (m, 0.5 H), 4.60–4.70 (m, 0.5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 20.6, 28.9, 29.6, 30.6, 31.7, 52.6, 55.5, 63.2, 63.3, 75.1, 80.2, 154.2, 155.3, 170.1, 170.2.

MS (EI, 70 eV): *m*/*z* (%) = 231 (1) $[M]^+$, 216 (19), 133 (8), 84 (100), 73 (21), 72 (26), 57 (30), 43 (40).

Anal. Calcd for $C_{10}H_{17}NO_3S$: C, 51.92; H, 7.41; N, 6.06; S, 13.86. Found: C, 51.91; H, 7.29; N, 5.95; S, 13.51.

Thiiran-2-ylmethyl Carbamates; General Procedure

N-Alkyl-5-(acyloxymethyl)-1,3-oxathiolan-2-imine **1** (9.7 mmol) was added to a soln of Na (20 mg, 0.9 mmol) in abs MeOH (20 mL). The mixture was stirred for 10 min at r.t. and then neutralized with AcOH (0.1 mL, 1.7 mmol). The solvent was removed in vacuo and the residue purified by column chromatography (silica gel, PE–CH_2Cl_2, 5:1). No chromatographic purification was required for the acetoxymethyl derivative.

(2*R*/*S*)-Thiiran-2-ylmethyl 1-Adamantylcarbamate (2a)

Yield: 2.15 g (83%); colorless powder; mp 64–65 °C.

IR (KBr): 3317, 2908, 1708, 1531, 1234, 1057 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.68 (m, 6 H), 1.84–1.96 (m, 6 H), 2.02–2.12 (m, 3 H), 2.25 (d, *J* = 7.2 Hz, 1 H), 2.50 (d, *J* = 7.2 Hz, 1 H), 3.04–3.17 (m, 1 H), 4.07 (d, *J* = 7.8 Hz, 2 H), 4.64 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 29.4, 31.6, 36.2, 41.0, 50.8, 68.0, 154.1.

MS (EI, 70 eV): *m*/*z* (%) = 267 (9) $[M]^+$, 234 (2), 196 (9), 135 (100), 73 (63), 72 (17), 45 (42).

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.78; H, 7.99; N, 5.15; S, 11.71.

(2*S*)-Thiiran-2-ylmethyl 1-Adamantylcarbamate (2a)

Yield: 2.20 g (85%); colorless powder; mp 62–63 °C; $[\alpha]_D^{20}$ –20.0 (*c* 1.04, CH_2Cl_2).

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.81; H, 7.90; N, 5.18; S, 11.69.

(2*R*)-Thiiran-2-ylmethyl *tert*-Butylcarbamate (2b)

Yield: 1.49 g (81%); pale-yellow oil; $[\alpha]_D^{20}$ +31.2 (*c* 1.11, CH_2Cl_2).

IR (KBr): 3348, 2970, 1728, 1712, 1269, 1080 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 2.19 (d, *J* = 7.2 Hz, 1 H), 2.45 (d, *J* = 7.2 Hz, 1 H), 3.00–3.10 (m, 1 H), 4.02 (d, *J* = 7.8 Hz, 2 H), 4.81 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 28.8, 31.4, 50.3, 67.9, 154.2.

MS (EI, 70 eV): *m*/*z* (%) = 189 (29) $[M]^+$, 118 (11), 90 (62), 73 (100), 72 (94), 57 (83), 45 (60).

Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99; N, 7.40; S, 16.94. Found: C, 50.71; H, 7.92; N, 7.33; S, 16.69.

X-ray Crystallographic Data of Compound 1a

$C_{21}H_{25}NO_3S$, M = 371.48, monoclinic, space group $P2_1$, *a* = 6.380(3) Å, *b* = 17.906(8) Å, *c* = 16.520(7) Å, β = 99.585(7)°, *V* = 1861.0(14) $Å^3$, *Z* = 4, D_c = 1.326 $g \cdot cm^{-3}$. Intensities of 10084 independent reflections were measured on a Bruker Smart 1000 CCD diffractometer, $2\theta \leq 59.9°$, λ[Mo-K_α] = 0.71073 Å. The structure was solved by the direct method and refined using full matrix least-squares on *F*2 using SHELXTL PLUS 5.10 software. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in the calculated positions and refined isotropically. The absolute crystal structure and absolute molecular configuration were determined using the Flack parameter [absolute structure parameter –0.07(5)]. The refinement converged to *R*1 = 0.049, *wR*2 = 0.110, GOF = 0.998 [7526 observed reflections with $I2 > 2\sigma(I)$]. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 783390 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk; or via www.ccdc.cam.uk/conts/retrieving.html.

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