Stereospecific 2*H*-Azirine Formation from the Modified Neber Reaction of Oxime Carbamates

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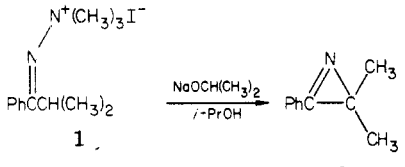
In the first reported synthesis of a 2*H*-azirine derivative from an oxime carbamate via a modified Neber reaction, (*E*)-1,1-bis(methylthio)-3,3-dimethyl-2-butanone *O*-[(methylamino)carbonyl]oxime was converted to the 2*H*-azirine derivative 3-*tert*-butyl-2-(methylthio)-2-(methylsulfonyl)-2*H*-azirine upon reaction with $KMnO_4$ or *m*-chloroperbenzoic acid. 2*H*-Azirine formation was shown to be dependent on the acidity of the α-hydrogen and the configuration of the starting oxime carbamate. Reaction of the corresponding *Z* isomer resulted only in oxidation at sulfur. This is the first report of configurational stereospecificity in a modified Neber reaction. The mechanistic implications of this reaction are discussed, and supporting evidence is provided.

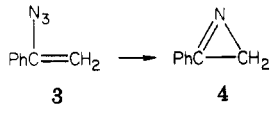
Over the last decade considerable interest has focused on the chemistry of 2*H*-azirines. A number of comprehensive reviews have been published, covering the synthesis and reactions of these highly strained and reactive heterocycles.[1] Two methods have been widely used in their synthesis. One has been based on a modified Neber reaction of quaternary hydrazonium salts. For example, Parcell and then later Nair reported the synthesis of 2,2-dimethyl-3-phenyl-2*H*-azirine (**2**) by treatment of isobutyrophenone *N*,*N*,*N*-trimethylhydrazonium iodide (**1**) with base, eq 1.[2] The scope of this reaction has been



(1)

1 **2**

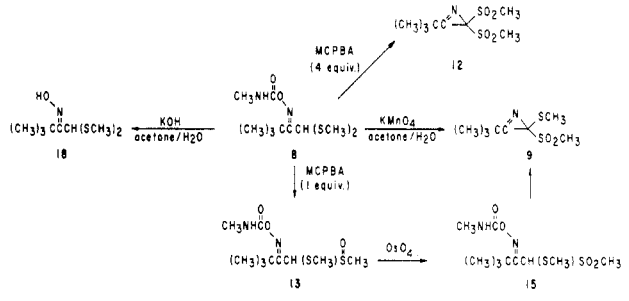
reported to be limited by the type of hydrogen available on the α-carbon.[3,6] Alternatively, the pyrolysis or photolysis of vinyl azides has been used in synthesizing 2*H*-azirines.[4] For example, Smolinsky reported that 1-azido-1-phenylethylene (**3**) thermally decomposes to 3-phenyl-2*H*-azirine (**4**) (eq 2).[4a,b] Other routes to the 2*H*-azirines have also been described.[4k-o]



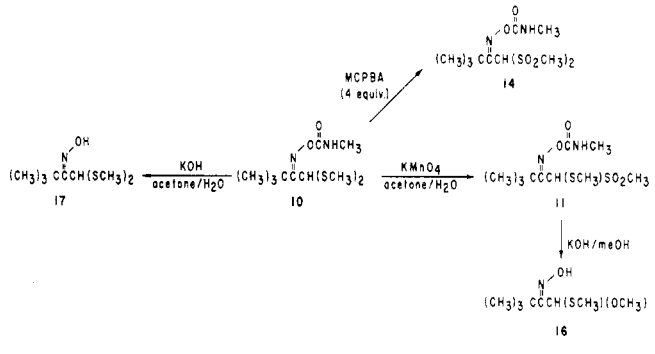
(2)

3 **4**

Scheme I



Scheme II



From mechanistic studies on the Neber reaction, the 2*H*-azirine has been shown to be a distinct intermediate formed by ring closure of a vinyl nitrene.[5] The evidence for the vinyl nitrene has resulted from the reported lack of stereospecificity in converting the *E* and *Z* isomers of *O*-tosyloximes to the same α-amino ketone.[5e] Although a vinyl nitrene has been suggested as a possible intermediate in the thermal and photochemical preparations of the azirine ring, direct evidence for such a species is lacking.[4a,d] We report a new oxidative synthesis of a functionalized 2*H*-azirine derivative from an α,α-bis(methylthio)oxime carbamate and that this reaction is the first report of a stereospecific 2*H*-azirine ring formation. It should be noted that Henery-Logan and Fridinger reported that the 2,2-dialkoxy-2*H*-azirine (**6**) was not produced when the trimethylhydrazonium iodide **5** was reacted with sodium isopropoxide in isopropyl alcohol.[6] The α-imino ortho

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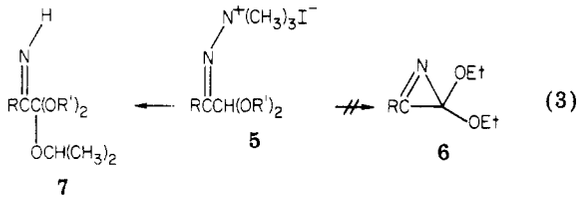
ester **7** was obtained instead, eq 3.



(3)

$R = CH_3$, $R' = C_2H_5$; $R = C_6H_5$, $R' = CH_2$

Reaction of an acetone solution of (*E*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)-carbonyl]oxime (**8**) with $KMnO_4$ gave an 81% yield of 3-*tert*-butyl-2-(methylsulfonyl)-2-(methylthio)-2*H*-azirine (**9**) (Scheme I). The 2*H*-azirine **9** was identified by ^1H NMR, IR, and mass spectra and by elemental analysis (see Experimental Section). A molecular weight (M_r) determination was found to be 227 ± 5% by vapor-phase osmometry in agreement with theory (M_r = 221). Reaction of the *Z* isomer **10** with $KMnO_4$ under identical conditions resulted in a 90% yield of (*Z*)-3,3-dimethyl-1-(methylsulfonyl)-1-(methylthio)-2-butanone *O*-[(methylamino)-carbonyl]oxime (**11**) (Scheme II). Similar permanganate oxidations at sulfur have been reported.[7]

The use of *m*-chloroperbenzoic acid (MCPBA) produced slightly different results. Four equivalents of MCPBA converted **8** to 3-*tert*-butyl-2,2-bis(methylsulfonyl)-2*H*-azirine (**12**). Reaction of **8** with only 1 equiv of MCPBA gave a 95% yield of the monosulfoxide **13** as a 7:1 diastereomeric mixture (Scheme I). When the *Z* isomer **10** was oxidized with 4 equiv of MCPBA, only oxidation at sulfur occurred with no 2*H*-azirine formation. (*Z*)-3,3-Dimethyl-1,1-bis(methylsulfonyl)-2-butanone *O*-[(methylamino)carbonyl]oxime (**14**) was produced in quantitative yield.[8]

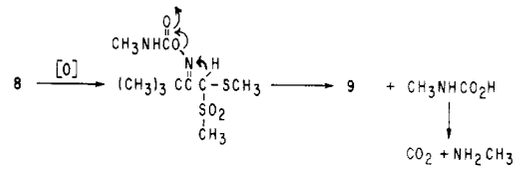
The mechanism of 2*H*-azirine formation is proposed to involve oxidation of a sulfur atom to give the monosulfone **15** as an intermediate (Scheme III). A 1,3-elimination of CH_3NHCO_2H from **15** would produce the 2*H*-azirine **9**. The elimination would be favored by the increased acidity of the methine proton resulting from sulfur oxidation. Consistent with this two-step process was the production of the *E* sulfone **15** by osmium tetraoxide oxidation of the *E* sulfoxide **13** (Scheme I).[9] Presumably, under the osmium tetraoxide reaction conditions employed, a suitable base was not present to cause elimination with azirine formation. The *E* sulfone **15** was extremely unstable. It was converted to the 2*H*-azirine **9** upon silica gel chromatography or upon attempts at recrystallization.

All attempts to convert the (*Z*)-3,3-dimethyl-1-(methylsulfonyl)-1-(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime (**11**) to the 2*H*-azirine **9** were unsuccessful. The reaction of **11** with methanolic KOH for 3 h at room temperature resulted in an 86% yield of 3,3-dimethyl-1-methoxy-1-(methylthio)-2-butanone oxime (**16**) (Scheme II). The presence of the 2*H*-azirine **9** in the reaction could not be detected by TLC. With a 10% excess of KOH in acetone–water, **11** decomposed to several unknown compounds with no trace of 2*H*-azirine production. The relatively facile loss of the methylsulfinate from **11** under the hydrolytic conditions was also unexpected. Although β and α eliminations of sulfones are well-known, nucleophilic displacements are not very common.[10] The reaction may involve hydrolysis to the oxime followed by an elimination to an α,β-unsaturated nitroso intermediate which would subsequently add methanol. Such eliminations have been suggested to occur under basic conditions in α-substituted oximes by Payne and co-workers.[11]

Reaction of the unoxidized carbamates **8** and **10** with a slight excess of potassium hydroxide in acetone effected a slow hydrolysis to give the corresponding oximes **18** and **17**, respectively, suggesting the need for a more acidic methine proton for azirine formation.

In summary, from these results we can conclude that it is unlikely that a nitrene intermediate is formed in the conversion of the oxime carbamate **8** to the 2*H*-azirine **9** under these oxidative conditions. This conclusion follows from the observed stereospecificity of the process and our inability to convert the *Z* sulfone **11** to 2*H*-azirine **9** under a variety of conditions.

Scheme III



Experimental Section

^1H NMR spectra were recorded on a Perkin-Elmer R24B spectrometer using Me_4Si as an internal standard. Natural-abundance ^{13}C NMR spectra were obtained on a Brucher WH-90 spectrometer at 22 MHz with complete proton decoupling in $CDCl_3$ for field/frequency locking, and chemical shifts were referenced to Me_4Si. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 137 infrared spectrometer. All boiling points and melting points are reported uncorrected. Mass spectra were recorded at 70 eV on a Varian CH-7 mass spectrometer interfaced with a Varian 1740 gas chromatograph. The synthesis and establishment of the configurations of the *E* and *Z* isomers of 3,3-dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)-carbonyl]oxime, i.e., compounds **8** and **10**, have been detailed.[12]

Preparation of 3-*tert*-Butyl-2-(methylsulfonyl)-2-(methylthio)-2*H*-azirine (9). To a cooled solution (ice bath) of 1.000 g (3.78 mmol) of (*E*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime (**8**) in 40 mL of acetone were added 0.38 g of magnesium sulfate and a solution of 0.88 g (5.6 mmol) of $KMnO_4$ in 18 mL of H_2O. The solution was stirred at 0 °C for 30 min, allowed to come to room temperature, and stirred for 20 h. The brown MnO_2 was removed by vacuum filtration and the filtrate concentrated by rotary evaporation to give 0.745 g of a brown semisolid. A ^1H NMR spectrum of this sample indicated 25% starting material and 75% 2*H*-azirine **9**; thus an 81% yield was obtained. Treatment with activated charcoal and recrystallization (hexane–acetone) resulted in 0.168 g of the 2*H*-azirine as a white solid: mp 68–69 °C; ^1H NMR ($CDCl_3$) δ 1.40 (9 H, s, *tert*-butyl), 2.38 (3 H, s, SCH_3), 3.07 (3 H, s, SO_2CH_3); IR (KBr) 2900 [a low-intensity C=N stretch at 1770 cm^{-1}; the literature reports C=N in 2*H*-azirines at 1770 cm^{-1}),[4e] 1300 and 1120 cm^{-1} (SO_2); mass spectrum, *m/e* (relative intensity) M^+ (not

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(8) All of the sulfur oxides, i.e., the mono-, di-, tri-, and tetraoxides, of (*Z*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)-carbonyl]oxime (**10**) have been prepared and found to be stable.

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observed), 142 (17), 85 (28), 69 (46), 57 (100), 41 (97). A molecular weight determination by vapor-phase osmometry indicated a compound with an M_r of 227 (±5%) (theory, M_r = 221). Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.4; H, 6.8; N, 6.3. Found: C, 43.1; H, 7.2; N, 6.2.

Preparation of (*Z*)-3,3-Dimethyl-1-(methylsulfonyl)-1-(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (11). (*Z*)-3,3-Dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime (10; 0.264 g, 1.00 mmol) was dissolved in 10 mL of acetone and the solution cooled to 0 °C. Magnesium sulfate (0.1 g) and a solution of potassium permanganate (0.21 g, 1.3 mmol in 3.5 mL of H_2O) were added, and the mixture was stirred for 0.5 h at 0 °C. The mixture was stirred 16 h at 23 °C, and the solids were removed by filtration. Concentration by rotary evaporation gave an oil that was dissolved in methylene chloride, dried ($MgSO_4$), and rotary evaporated to yield 0.280 g (95% yield) of the monosulfone as a white solid. Recrystallization from acetone–hexane gave 0.20 g of product: mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 6.25 (1 H, br, NH), 4.27 (1 H, s, CH), 3.51 (3 H, s, SO_2CH_3), 2.91 (3 H, d, J = 4.8 Hz, NCH_3), 2.46 (3 H, s, SCH_3), 1.29 (9 H, s, *tert*-butyl); ^{13}C NMR (acetone-d_6) δ 164.4 (C=N), 154.8 (C=O), 71.1 (CH), 40.4 (SO_2CH_3), 39.0 (Cq), 27.7 ($(CH_3)_3$), 18.4 (SCH_3); mass spectrum, m/e (relative intensity) 296 (0.06, M^+), 239 (0.25), 217 (9.5), 192 (0.2), 160 (10), 159 (11), 144 (9), 134 (2), 129 (3), 114 (2), 104 (2), 99 (2.5), 86 (29), 77 (38), 57 (100), 41 (30); IR (KBr) 3320 (NH), 2925 (CH), 1720 (C=O), 1620 (C=N), 1500, 1410, 1365, 1290 and 1110 (SO_2), 1225, 1060, 940, 900, 818, 800, 770, 640, 620, 600 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_4S_2$: C, 40.52; H, 6.80; N, 9.45. Found: C, 40.6; H, 7.0; N, 9.4.

Preparation of 3-*tert*-Butyl-2,2-bis(methylsulfonyl)-2*H*-azirine (12). (*E*)-3,3-Dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime (8; 0.133 g, 0.503 mmol) was dissolved in 10 mL of methylene chloride and the solution cooled to 0 °C. Powdered *m*-chloroperbenzoic acid (0.430 g, 2.49 mmol) was added, and the mixture was stirred at 0 °C for 16 h and allowed to come to room temperature. The mixture was cooled to −78 °C and the *m*-chlorobenzoic acid removed by filtration. The filtrate was concentrated to give a mixture of azirine and *m*-chlorobenzoic acid (by ^{1}H NMR). A chloroform solution of the crude solids was passed through a column of basic alumina to remove the residual *m*-chlorobenzoic acid. The eluent was rotary evaporated to yield 90 mg (55% yield) of the azirine as a white solid. Recrystallization from carbon tetrachloride gave 65 mg of the azirine as a white crystalline solid: mp 127–130 °C; ^{1}H NMR (acetone-d_6) δ 1.47 (9 H, s, *tert*-butyl), 3.32 (6 H, s, SCH_3); IR (KBr) 3008, 2980, and 2925 (CH), 1768 (C=N), 1460, 1330, and 1140 (SO_2), 978, 965, 758, 750 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_4S_2$: C, 37.9; H, 6.0; N, 5.5. Found: C, 37.8; H, 6.2; N, 5.6.

Preparation of (*E*)-3,3-Dimethyl-1-(methylsulfinyl)-1-(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (13). To a cooled (ice bath) solution of 4.32 g (16.4 mmol) of (*E*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime (8) in 100 mL of CH_2Cl_2 was added 3.60 g of *m*-chloroperbenzoic acid (80.5%) in 30 mL of CH_2Cl_2. The solution was allowed to come to room temperature and stir 18 h. Washing with two portions of saturated $NaHCO_3$ solution and 5 mL of H_2O, drying (Na_2SO_4), and concentrating the solution by rotary evaporation resulted in 4.35 g (100%) of the monosulfoxide as a diastereomeric mixture (ratio 7:1). Recrystallization from acetone–ether gave 2.11 g of a single diastereomer as a white crystalline solid: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 6.50 (1 H, br s, NH), 4.36 (1 H, s, CH), 2.80 (3 H, d, J = 4.5 Hz, NCH_3), 2.88 (3 H, s, $SOCH_3$), 2.18 (3 H, s, SCH_3), 1.40 (9 H, s, *tert*-butyl); ^{13}C NMR ($CDCl_3$) δ 163.02 (C=N), 155.32 (C=O), 66.99 (CH), 38.11 (Cq), 36.91 ($S(O)CH_3$), 27.94 (NCH_3), 27.52 ($(CH_3)_3$), 12.67 (SCH_3); IR (KBr) 3380 (NH), 2950 and 2910 (CH), 1735 (CO), 1600 (C=N), 1480, 1400, 1200, 1035, 960, 935 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_3S_2$: C, 42.8; H, 7.2; N, 10.0. Found: C, 42.8; H, 7.5; N, 9.8.

Preparation of (*Z*)-3,3-Dimethyl-1,1-bis(methylsulfonyl)-2-butanone *O*-[(Methylamino)carbonyl]oxime (14). (*Z*)-3,3-Dimethyl-1,1-bis(methylthio)-2-butanone *O*-[methylamino)carbonyl]oxime (7; 9.24 g, 35.0 mmol) was dissolved in 50 mL of methylene chloride and the solution cooled to 0 °C. A solution of *m*-chloroperbenzoic acid (Aldrich; 85%, 30.45 g, 150.0 mmol) in 350 mL of methylene chloride was added during 20 min. The mixture was stirred 16 h at 22 °C and then cooled to −78 °C. The precipitated *m*-chlorobenzoic acid was removed by filtration. The filtrate was rotary evaporated to yield 12.2 g of white solid. ^{1}H NMR indicated a mixture of 14 and *m*-chlorobenzoic acid. The solid was recrystallized from hexane–acetone to yield 4.35 g (38% yield) of 14 as colorless prisms: mp 167–171 °C dec; ^{1}H NMR (acetone-d_6) δ 6.50 (1 H, br, NH), 5.60 (1 H, s, CH), 3.42 (6 H, s, SO_2CH_3), 2.82 (3 H, d, J = 4.5 Hz, NCH_3) 1.28 (9 H, s, *tert*-butyl); ^{13}C NMR (acetone-d_6) δ 157.1 (C=N), 154.2 (C=O), 83.4 (CH), 45.3 (SO_2CH_3), 39.9 (Cq), 28.0 ($(CH_3)_3$); mass spectrum, m/e (relative intensity) 328 (0.3, M^+), 271 (16), 254 (13), 192 (85), 191 (65), 186 (4), 161 (93), 143 (75), 100 (14), 99 (33), 97 (48), 94 (16), 83 (36), 81 (98), 77 (25), 69 (28), 63 (23), 58 (54), 57 (100), 55 (38), 41 (79), 28 (29); IR (KBr) 3365 (NH), 2910 (CH), 1730 (C=O), 1620 (C=N), 1500, 1400, 1300 and 1120 (SO_2), 1225, 945, 915, 820, 750, 605 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_6S_2$: C, 36.57; H, 6.14; N, 8.53. Found: C, 36.7; H, 6.4; N, 8.7.

Preparation of (*E*)-3,3-Dimethyl-1-(methylsulfonyl)-1-(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (15). To 0.282 g (1.01 mmol) of the monosulfoxide 13 in 20 mL of CCl_4 was added a solution of 0.262 g of OsO_4 (**Caution**: very toxic) in 3 mL of CCl_4. The addition was made dropwise over a 5–10-min period. A black precipitate formed. The mixture was stirred at 25 °C for 2 h, filtered, and concentrated. The black oil was redissolved in Et_2O, filtered, and washed with a $NaHSO_3$ solution. The ether solution (light brown) was dried (Na_2SO_4), filtered, and concentrated. Treatment with ether, filtering, and concentrating three times gave 100 mg of the desired sulfone: ^{1}H NMR ($CDCl_3$) δ 1.40 (9 H, s, *tert*-butyl), 2.42 (3 H, s, SCH_3), 2.80 (3 H, d, J = 4 Hz, NCH_3), 3.71 (3 H, s, SO_2CH_3), 4.55 (1 H, s, CH), 6.04 (1 H, br, NH); IR (neat) 3380 (NH), 3000, 2960, 2940, and 2880 (CH), 1740 (C=O), 1620 (C=N), 1510, 1420, 1360, 1300, 1230, 1150, 1110, 1090, 940, 750 cm^{-1}. This material was unstable and was converted to the 2*H*-azirine 9 upon attempted crystallization from heptane–CH_2Cl_2 or when chromatographed, i.e., thick layer or column.

Reaction of (*Z*)-3,3-Dimethyl-1-(methylsulfonyl)-1-(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (11) with Methanolic Potassium Hydroxide. To 0.946 g (16.9 mmol) of potassium hydroxide (85%) dissolved in 30 mL of 83% aqueous methanol (by volume) was added a solution of 0.500 g of the *Z* sulfone 11 dissolved in 10 mL of methanol. The course of the reaction was monitored by TLC (silica gel; 1:1 ether–hexane; UV and I_2). After being stirred at room temperature for 3 h, the reaction mixture was reduced to half its volume by rotary evaporation and then extracted with two portions of ether. Drying (Na_2SO_4) and concentrating the ethereal solution gave 0.34 g of solids. Recrystallization (heptane) resulted in 0.28 g (86% yield) of (*Z*)-3,3-dimethyl-1-(methoxy)-1-(methylthio)-2-butanone oxime (16) as a white crystalline solid: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (9 H, s, *tert*-butyl), 2.33 (3 H, s, SCH_3), 3.46 (3 H, s, OCH_3), 5.45 (1 H, s, CH), 9.65 (1 H, br, s, OH); IR (KBr) 3265 (OH), 2950 and 2900 (CH), 1460, 1420, 1375, 1200, 1090, 790 cm^{-1}; mass spectrum, m/e 191 (M^+), 159, 144, 143, 91, 61, 57. Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.3; H, 8.9; N, 7.3. Found: C, 49.2; H, 9.1; N, 7.2. No azirine was observed in the reaction mixture by ^{1}H NMR or by TLC.

Hydrolysis of (*E*)-3,3-Dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (8). A total of 0.203 g (0.768 mmol) of 8 was dissolved in 12.5 mL of 1 M methanolic potassium hydroxide. After being stirred at room temperature for 56 h, the solution was concentrated to about 5 mL and extracted with methylene chloride. After the methylene chloride extracts were dried ($MgSO_4$) and concentrated, 0.195 g of residue was obtained. Thick-layer chromatography (silica gel, 1:1 ether–hexane) resulted in 0.045 g (22%) of the starting carbamate and 0.050 g (31%) of (*E*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone oxime (18) as white crystals: mp 121–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (9 H, s, *tert*-butyl), 2.05 (6 H, s, SCH_3), 4.53 (1 H, s, CH), 9.29 (1 H, s, OH); IR (KBr) 3250 (OH), 2950 and 2900 (CH), 1620 (C=N), 1400, 1220, 1100, 1000, 950 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 163.2 (CN), 51.2 (CH), 37.3 (Cq), 28.2 ($(CH_3)_3$), 17.5 (SCH_3); mass spectrum, m/e (relative intensity) 207 (23, M^+), 161 (15), 160 (86), 159 (51), 144 (8), 143 (23), 142 (8), 107 (22), 104

(6), 88 (5), 87 (23), 86 (60), 81 (6), 77 (20), 59 (11), 57 (100), 41 (59). Anal. Calcd for $C_3H_7NOS_2$: C, 46.3; H, 8.3; N, 6.8. Found: C, 46.4; H, 8.7; N, 6.7. No 2*H*-azirine could be detected by TLC.

Hydrolysis of (*Z*)-3,3-Dimethyl-1,1-bis(methylthio)-2-butanone *O*-[(Methylamino)carbonyl]oxime (10). A total of 0.203 g (0.768 mmol) of **10** was dissolved in 12.5 mL of 1 M methanolic potassium hydroxide. After being stirred at room temperature 2.5 h, the solution was concentrated to ca. 5 mL and extracted with CH_2Cl_2. After the organic extracts were dried ($MgSO_4$) and concentrated, 0.162 g of solid residue was obtained. ^1H NMR indicated a 1:1 mixture of starting carbamate and (*Z*)-3,3-dimethyl-1,1-bis(methylthio)-2-butanone oxime (**17**). The oxime was isolated by thick-layer chromatography as a white crystalline solid: mp 122-128 °C; ^1H NMR ($CDCl_3$) δ 9.29 (1 H, s, OH), 4.27 (1 H, s, CH), 2.28 (6 H, s, SCH_3), 1.23 (9 H, s, *tert*-butyl); IR (neat) 3250 (OH), 2900 and 2850 (CH), 1620 (N=C), 1420, 1400, 1350, 1240, 1160, 950, 880 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 163.19 (C=N), 51.23 (CH), 37.33 (Cq), 28.23 ($(CH_3)_3$), 17.51 (SCH_3); mass spectrum, *m/e* (relative intensity) 207 (19, M^+), 161 (22), 160 (78), 159 (99), 144 (30), 143 (9), 129 (12), 107 (45), 86 (31), 77 (73), 57 (100), 41 (62). Anal. Calcd for $C_8H_{17}NOS_2$: C, 46.3; H, 8.3; N, 6.8. Found: C, 46.6; H, 8.5; N, 6.7.

Registry No. **8**, 73926-56-4; **9**, 73926-57-5; **10**, 73926-58-6; **11**, 73940-61-1; **12**, 73926-59-7; **13** (isomer 1), 73926-60-0; **13** (isomer 2), 73940-62-2; **14**, 73926-61-1; **15**, 73926-62-2; **16**, 73926-63-3; **17**, 73926-64-4; **18**, 73926-65-5.

4,5,6,7-Tetrahydrobenzo[*b*]thiophenes via Diisobutylaluminum Hydride Mediated Detosylation Reactions

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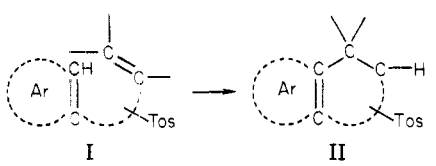
A novel synthesis of 4,4-dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3a**), its 7-substituted derivatives **3b-d** and also 7,7-dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**12b**) is presented. The strategy centers on the facile diisobutylaluminum hydride mediated detosylation of precursors **2a-d** and **12a**. Some of the latter, such as **2a,b** and **12a**, are cleanly and efficiently prepared by FSO_3H-SO_2 induced cycloalkylation of **1a,b** and **11b**. The others, **2c** and **2d**, are derived from **2a** via phase-transfer alkylation techniques. A number of approaches toward open systems **1a-d** are described.

The synthetic power of the sulfone group has recently been reviewed.[1] The *p*-toluenesulfonyl group (tosyl, Tos), in particular, is currently drawing attention because of its role in modern carbon-carbon bond construction. When on carbon, it enhances existing C-H acidity and stabilizes a subsequently generated carbanion. These react with carbon electrophiles, after which the tosyl fragment, having served its purpose, is removed. In this sense the tosyl group is unique in that it stabilizes a carbanion on the carbon to which it is attached, while being of sufficient nucleofugicity to allow its replacement by hydrogen.[2] In practice tosyl derivatives are easily manipulated substances, readily identified by methyl NMR signals around 2.40 ppm.

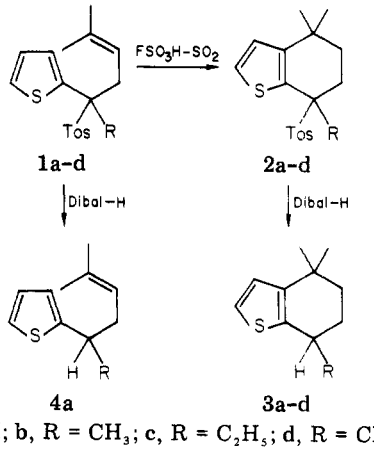
A strategy incorporating ring closures of pretosylated alkyl aromatic systems such as I to derivatives II seems to have no recorded precedent. It would offer intriguing prospects in providing structures predisposed to the manipulations given above. We decided to examine this possibility.



I II

Thiophene-based models were chosen since cycloalkylation onto thiophene is known to occur readily;[3] moreover, the resulting benzo[*b*]thiophenes comprise an area of past involvement of one of us.[4] Realization of the objective would hinge on elaborating reaction conditions of sufficient power to bring about ring closure, yet mild enough to allow the tosyl group to come through unscathed. Such a method is now described; conditions are presented for obtaining **2a,b** from **1a,b**. In addition, a novel C-detosylation method featuring the use of diisobutylaluminum hydride (Dibal-H) has been found to remove tosyl fragments from thiophene systems **1a** and **2a-d** (Scheme I).

Scheme I



a, R = H; b, R = CH_3; c, R = C_2H_5; d, R = $CH_2C_6H_5$

(1) P. D. Magnus, *Tetrahedron*, **33**, 2019 (1977).

(2) Another such fragment is the cyano moiety; for example, treatment of tetradecylnitrile with lithium in ethylamine gives, besides reduction to the tetradecylamine, also decyanation to tridecane: P. G. Arapakos, M. K. Scott, and F. E. Huber, Jr., *J. Am. Chem. Soc.*, **91**, 2059 (1969).

(3) See, for instance, B. Iddon and R. M. Scrowston in *Adv. Heterocycl. Chem.*, **11**, 177-381 (1970).

(4) (a) E. F. Godefroi, U.S. Patent 3 111 527 (1963); *Chem. Abstr.*, **60**, 2895 (1964); (b) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 1056 (1973).

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