Synthesis and Reaction of 5,6,7,8-Tetrahydro-4*H*-oxazolo[4,5-*c*]azepin-4-ones

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The synthesis of 5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepin-4-ones **5a**,**b** and 1,3-benzoxazol-4-amines **4a**,**b** are described starting from 4,5,6,7-tetrahydro-1,3-benzoxazol-4-ones. Thionation of **5a**,**b** followed by alkylation with ethyl bromoacetate led to the corresponding *S*-alkyl azepines **7a**,**b**.

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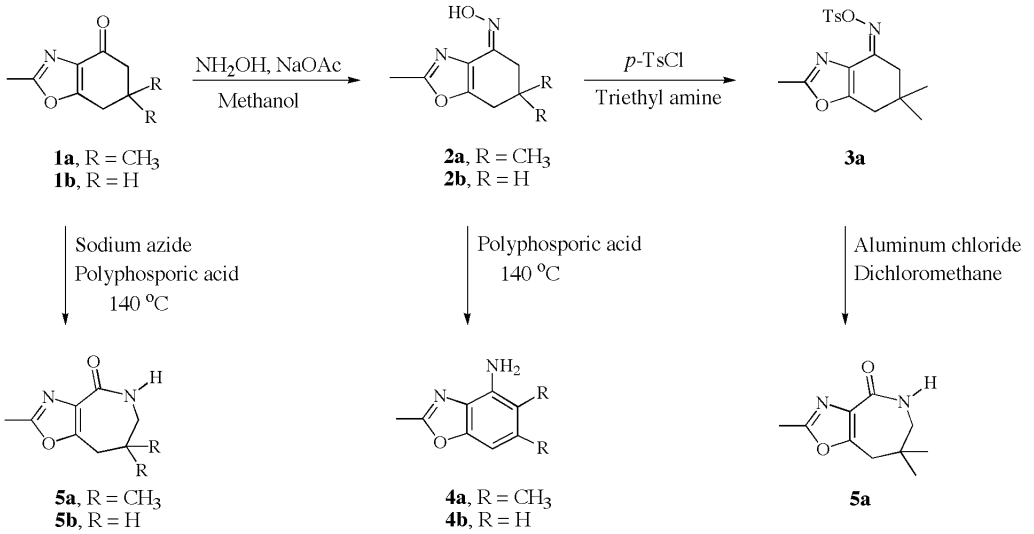
There has been much interest in the synthesis of heterocyclofused-azepines over the past decade due to their physiological and biological activities [1,2,3]. As part of a program directed towards the synthesis and evaluation of biological activities of *N*-containing heterocycles, we exploited the synthesis and reaction of 5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepin-4-one.

Recently Cortés reported that rearrangement of 4,5,6,7-tetrahydrobenzofuran-4-one oxime in polyphosphoric acid underwent a clean Beckmann rearrangement with alkyl migration to give the 4,5,7,8-tetrahydrofuro[3,2-*c*]azepin-4-one in 80% yield [2d]. Also Sucrow demonstrated that 3-aryl-1-methyl-4,5,6,7-tetrahydro-1*H*-indazolone oximes gave on treatment with polyphosphoric acid Semmler-Wolff rearrangement to the 4-aminoindazoles, Beckmann rearrangement of the oxime sulfonates led to the 1-methyl-1,4,5,6,7,8-hexahydropyrazolo[4,3-*b*]azepin-5-ones, whereas Schmidt reaction with the free indazolones gave the isomeric 1-methyl-1,4,5,6,7,8-hexahydropyrazolo-[4,3-*c*]azepin-4-ones [2c].

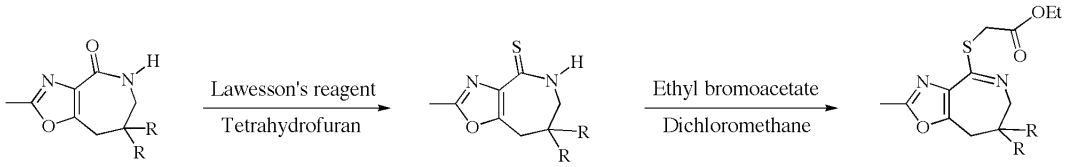
Our starting material 4,5,6,7-tetrahydro-1,3-benzoxazol-4-one **1** was prepared by the rhodium catalyzed reaction of 2-diazo-1,3-carbonyl compounds such as diazodimedone and 2-diazo-1,3-cyclohexandione with acetonitrile [4]. The initial attempt to convert **1** into **5** was carried out under Beckmann rearrangement conditions [5] as shown in Scheme 1. Treatment of oxime **2a** obtained from the reaction of 2,6,6-trimethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one **1a** with hydroxylamine hydrochloride in polyphosphoric acid yielded the single 2,5,6-trimethyl-1,3-benzoxazol-4-amine **4a** in 80% yield. The structure of **4a** was established from its spectral characteristics. In the ir spectrum of **4a** a N-H stretching band was observed at 3453 - 3345 cm^{-1}. In the ^1H nmr spectrum of **4a** three singlets for the C-2, -5 and -6 methyl groups at δ 2.12, 2.34 and 2.57, and one deuterium oxide exchangeable singlet at δ 4.15 corresponding to the NH_2 can be observed together with a singlet for the =CH proton of the benzoxazole ring at δ 6.73. This structure was also confirmed by a mass spectrum and an elemental analysis.

Due to hydrogen bonding of the hydroxyamino group with the oxazole nitrogen, the oxime **2** appears to be the (*Z*)-configuration in polyphosphoric acid. Thus the electrons of the α C-H bond approach the developing nitrenium ion as the N-O bond synchronously dissociated with the formation of an intermediate azirine. Aromatization to the 4-aminobenzoxazole **4** follows on protonation of the azirine nitrogen with subsequent ring

Scheme 1



Scheme 2



5a, R = CH_3
5b, R = H

6a, R = CH_3
6b, R = H

7a, R = CH_3
7b, R = H

opening to the imine and proton transfer [6]. Also, exclusive methyl migration from C-6 to C-5 was observed during the aromatization for compound **2a**.

The aluminum chloride promoted rearrangement [7] of oxime sulfonate **3a** obtained from **2a** and *p*-toluenesulfonyl chloride in dichloromethane at -40° resulted in the formation of 2,7,7-trimethyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]-azepin-4-one **5a** in 70% yield. The structure of **5a** was confirmed by spectral and analytical data. In the ir spectrum, the N-H absorption band and the conjugated carbonyl absorption band was observed at 3214 and 1662 cm^{-1}, respectively. Most characteristic in the nmr spectrum of **5a** was a broad signal at δ 8.21 for N-H proton and doublet signal at δ 3.14 (J = 6.0 Hz) for the methylene protons at C-6 next to amide nitrogen and carbon signal at δ 51.7 for the C-6 in the ^1H and ^{13}C nmr. The mass spectrum of **5a** also revealed a corresponding molecular ion peak at m/z 194 (100% relative abundance). This two-step sequence provided **5a** in 39% yield from **1a**.

Under Schmidt conditions [8], we could obtained oxazolo[4,5-*c*]azepines **5**, *i.e.* treatment of 2,6,6-trimethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one **1a** with sodium azide in polyphosphoric acid provided **5a** in 40% yield.

To explore reactivity of these new oxazolo[4,5-*c*]azepin-4-ones, a chemical transformation was next examined shown in Scheme 2. Compound **5** was treated with Lawesson's reagent in refluxing tetrahydrofuran to afford azepine-4-thione **6** in 80-86% yield. The infrared spectrum of **6a** displayed absorption bands at 3257 and 1529 cm^{-1} which were assignable to N-H and C=S stretching, respectively. In the ^1H nmr spectra of **6a** the presence of one broad signal at δ 9.47, consistent with the presence of a thioamide group; the other two proton signals at δ 3.24 (d, J = 6.0 Hz) and 2.78 (singlet) were assignable to the methylene protons at C-6 and C-8. The mass spectrum of **6a** showed the molecular ion at m/z 210 (100% relative abundance). Alkylation of **6** with ethyl bromoacetate in the presence of sodium hydrogen carbonate led to the *S*-alkylated compound **7**. The structure of **7** was characterized by ir, nmr and mass spectra. Due to the instability of **7** in air, microanalysis did not give satisfactory results.

Thus, oxazolo[4,5-*c*]azepin-4-ones were prepared by Schmidt rearrangement, further investigations on the biological activity and the synthesis of novel compounds from oxazolo[4,5-*c*]azepin-4-one are presently being carried out.

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were obtained using a Varian Unity Plus 300 instrument. The chemical shifts in the ^1H nmr spectra are reported in δ units downfield from the internal tetramethylsilane. The ir spectra were measured with a Galaxy FT-IR 7000 spectrophotometer. Mass spectra were recorded on either a Shimadzu QP-1000 spectrometer or a VG Quattro II spectrometer. Elemental analyses were performed on a Calro Erba 1106 by the Center for Scientific Instruments at Kyungpook National University. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses (tlc) were carried out on Merck silica gel $60F_{254}$ plates, visualizing with a 254-nm uv lamp. For routine column chromatography, Merck silica gel (70-230 mesh) was used as the adsorbents. All reactions were carried out under an atmosphere of argon. Organic chemicals were purchased from Aldrich Chemical Co and used as received. 2,6,6-Trimethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one (**1a**) and 2-methyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one (**1b**) were prepared by literature method [4].

2,6,6-Trimethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one Oxime (**2a**).

A mixture of **1a** (101 mg, 0.56 mmole), hydroxylamine hydrochloride (47 mg, 0.67 mmole) and sodium acetate (55 mg, 0.67 mmole) in 50 ml of methanol was refluxed for 4 hours. After the solvent was removed, the residue was neutralized with 20 ml of saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was recrystalized from dichloromethane and hexane to yield a white solid **2a** (62 mg, 57% yield). mp 194-195°; R_f 0.26 (ethyl acetate-hexane, 2:1); ir (potassium bromide) 3166, 2965, 1583, 1398, 934, 803 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 10.46 (s, 1H, NO*H*), 2.57 (s, 2H, H-7), 2.54 (s, 2H, H-5), 2.43 (s, 3H, CH_3), 1.09 (s, 6H, (CH_3)$_2$); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 160.0, 150.2, 146.4, 129.1, 35.1, 34.4, 31.9, 27.8, 13.0; ms: m/z 194 (M^+, 47), 179 (32), 138 (61), 109 (100).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 62.02; H, 7.39; N, 14.66.

2-Methyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one Oxime (**2b**).

The procedure to prepare **2b** was the same as for the preparation of **2a** starting with 659 mg (4.36 mmoles) of **1b**, hydroxylamine hydrochloride (349 mg, 5.02 mmoles) and sodium acetate (414 mg, 5.02 mmoles). Compound **2b** was obtained as a colorless solid in 50% yield; mp 186-188° (dichloromethane-hexane); R_f 0.17 (ethyl acetate-hexane, 2:1); ir

(potassium bromide) 3173, 2933, 1581, 1382, 1280, 1220, 936, 900 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.33 (s, 1H, NO*H*), 2.70-2.76 (m, 4H, H-5,7), 2.45 (s, 3H, CH_3), 1.94-2.03 (m, 2H, H-6); ^{13}C nmr (deuteriochloroform): δ 160.0, 151.3, 147.9, 130.1, 21.4, 20.9, 20.8, 13.6; ms: m/z 166 (M^+, 100), 150 (20), 138 (37), 122 (37).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.60; H, 6.36; N, 17.11.

2,6,6-Trimethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one Oxime Tosylate (**3a**).

To a solution of **2a** (2.12 g, 10.92 mmoles) and triethylamine (2.28 ml) in 25 ml of tetrahydrofuran was added a solution of *p*-toluenesulfonyl chloride (3.13 g, 16.42 mmoles) in 15 ml of tetrahydrofuran at 0° for 5 hours. After reaction was completed, the solvent was evaporated. The residue was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:2) to give **3a** (2.10 g, 55 %). mp 90°; ^1H nmr (deuteriochloroform): δ 7.93 (d, J = 8.1 Hz, 2H, *o-H* of Ph), 7.32 (d, J = 8.1 Hz, 2H, *m-H* of Ph), 2.64 (s, 2H, H-7), 2.58 (s, 2H, H-5), 2.45 (s, 3H, CH_3), 2.42 (s, 3H, 2-CH_3), 1.08 (s, 6H, (CH_3)$_2$); ms: m/z 348 (M^+, 4), 241 (14), 227 (20), 177 (4), 172 (19), 155 (25), 91 (100).

Anal. Calcd. for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found C, 58.83; H, 5.92; N, 8.34; S, 9.45.

2,5,6-Trimethyl-1,3-benzoxazol-4-amine (**4a**).

A mixture of **2a** (107 mg, 0.55 mmole) and polyphosphoric acid (4.0 ml) was mechanically stirred at 140° for 30 minutes. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:4) to give **4a** (78 mg, 80%), which was recrystalized from dichloromethane and hexane; mp 138-139°; R_f 0.35 (ethyl acetate-hexane, 1:1); ir (potassium bromide) 3453, 3345, 1638, 1240 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.73 (s, 1H, H-7), 4.15 (bs, 2H, N*H*), 2.57 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.12 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 160.8, 149.6, 135.6, 133.7, 128.1, 114.7, 101.0 (C-7), 21.3 (*C*H_3), 14.4 (*C*H_3), 12.5 (*C*H_3); ms: m/z 176 (M^+, 100), 161 (81), 106 (19).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.95; H, 6.91; N, 15.74.

2-Methyl-1,3-benzoxazol-4-amine (**4b**).

The procedure to prepare **4b** was the same as for the preparation of **4a** starting with 101 mg (0.61 mmole) of **2b** and 4.5 ml of polyphosphoric acid. Compound **4b** was obtained as a colorless solid in 51% yield; mp 76-77° (dichloromethane-hexane); R_f 0.35 (ethyl acetate-hexane, 1:1); ir (potassium bromide) 3424, 3339, 1640, 1241 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.07 (t, J = 7.8 Hz, 1H, H-6), 6.85 (d, J = 7.8 Hz, 1H, H-7), 6.55 (d, J = 7.8 Hz, 1H, H-5), 4.25 (bs, 2H, N*H*), 2.60 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 161.5, 151.9, 138.3, 129.5, 125.1, 108.7, 100.0 (C-7), 14.4 (*C*H_3); ms: m/z 148 (M^+, 100), 130 (5), 107 (10).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.75; H, 5.48; N, 19.12.

2,7,7-Trimethyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepin-4-one (**5a**).

Method 1

To a mixture of sodium azide (869 mg, 13.36 mmoles) in polyphosphoric acid (50 ml) was added 2.0 g (11.16 mmoles) of **1a**, and the mixture was mechanically stirred at 140° for 30 minutes. The mixture was neutralized with saturated sodium hydrogen carbonate solution and extracted three times with dichloromethane (30 ml). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was recrystalized from ethyl acetate and dichloromethane to give **5a** (866 mg, 40 % yield); mp 209-210°; R_f 0.45 (methanol-ethyl acetate, 1:2); ir (potassium bromide) 3214, 2963, 1662, 1482, 1272, 1077 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.21 (bs, 1H, N*H*), 3.14 (d, J = 6.0 Hz, 2H, H-6), 2.74 (s, 2H, H-8), 2.44 (s, 3H, CH_3), 1.10 (s, 6H, (CH_3)$_2$); ^{13}C nmr (deuteriochloroform): δ 165.2 (*C*O), 160.4, 153.3, 129.3, 51.7 (C-6), 40.2 (C-7), 31.3 (C-8), 26.4 ((*C*H_3)$_2$), 13.4 (*C*H_3); ms: m/z 194 (M^+, 100), 179 (59), 164 (26), 151 (64), 136 (10), 123 (31), 110 (29).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 62.08; H, 7.46; N, 14.61.

Method 2

To a stirred solution of **3a** (1.03 g, 2.96 mmoles) in 20 ml of dichloromethane was added aluminum chloride (1.18 g, 8.88 mmoles) at -40°. After 30 minutes, the cooling bath was removed and the mixture was stirred for 3 hours at room temperature. After the reaction mixture was carefully quenched by addition of water, extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was recrystallized from dichloromethane and hexane to give **5a** (711 mg, 70 %).

2-Methyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepin-4-one (**5b**).

The procedure to prepare **5b** was the same as for the preparation of **5a** starting with 4.63 g (30.63 mmoles) of **1b** and sodium azide (2.41 g, 37.08 mmoles) in polyphosphoric acid (70 ml). Compound **5b** was obtained as a colorless solid (dichloromethane-hexane) in 42% yield; mp 198°; R_f 0.34 (methanol-ethyl acetate, 1:2); ir (potassium bromide) 3209, 2931, 1672, 1650, 1478, 1294 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.52 (bs, 1H, N*H*), 3.40 (m, 2H, H-6), 2.95 (t, J = 6.9 Hz, 2H, H-8), 2.45 (s, 3H, CH_3), 2.09 (m, 2H, H-7); ^{13}C nmr (deuteriochloroform): δ 165.0 (*C*O), 160.0, 154.1, 129.5, 41.1 (C-6), 26.0 (C-7), 24.5 (C-8), 13.2 (*C*H_3); ms: m/z 166 (M^+, 73), 137 (19), 109 (29).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.10; H, 6.26; N, 17.06.

2,7,7-Trimethyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine-4-thione (**6a**).

To a suspension of **5a** (299 mg, 1.54 mmoles) in 50 ml of tetrahydrofuran was added Lawesson's reagent (747 mg, 1.85 mmoles). After the mixture was refluxed for 4 hours, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate-hexane, 2:1) to give **6a** (279 mg, 86%), which was recrystalized from dichloromethane and hexane; mp 211-212°; R_f 0.24 (ethyl

acetate); ir (potassium bromide) 3257, 2960, 1613, 1529, 1357, 1262, 963 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.47 (bs, 1H, N*H*), 3.24 (d, J = 6.0 Hz, 2H, H-6), 2.78 (s, 2H, H-8), 2.47 (s, 3H, CH_3), 1.10 (s, 6H, (CH_3)$_2$); ^{13}C nmr (deuteriochloroform): δ 190.0 (*C*S), 160.5, 150.5, 133.5, 56.0 (C-6), 40.4 (C-7), 31.9 (C-8), 26.4 ((*C*H$_3$)$_2$), 13.6 (*C*H$_3$); ms: m/z 210 (M^+, 100), 195 (55), 167 (14), 155 (36), 126 (49).

Anal. Calcd. for $C_{10}H_{14}N_2OS$: C, 57.12; H, 6.71; N, 13.32; S, 15.25. Found: C, 57.30; H, 6.36; N, 13.11; S, 15.20.

2-Methyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine-4-thione (**6b**).

The procedure to prepare **6b** was the same as for the preparation of **6a** starting with 2.06 g (12.40 mmoles) of **5b** and 6.33 g (15.65 mmoles) of Lawesson's reagent. Compound **6b** was obtained as a yellowish solid (dichloromethane-hexane) in 80% yield; mp 192-193°; R_f 0.14 (ethyl acetate-hexane, 1:9); ir (potassium bromide) 3154, 2961, 1607, 1527, 1283, 922 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.80 (bs, 1H, N*H*), 3.54 (m, 2H, H-6), 2.99 (t, J = 7.0 Hz, 2H, H-8), 2.48 (s, 3H, CH_3), 2.13 (m, 2H, H-7); ^{13}C nmr (deuteriochloroform): δ 189.2 (*C*S), 160.0, 151.4, 133.4, 45.4 (C-6), 26.0 (C-7), 23.3 (C-8), 13.2 (*C*H$_3$); ms: m/z 182 (M^+, 100), 153 (21), 125 (26), 95 (27).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37; S, 17.59. Found: C, 52.82; H, 5.45; N, 15.76; S, 17.57.

Ethyl 2-[(2,7,7-Trimethyl-7,8-dihydro-6*H*-azepino[3,4-*d*][1,3]-oxazol-4-yl)sulfanyl] acetate (**7a**).

A solution of **6a** (161 mg, 0.77 mmole) and ethyl bromoacetate (153 mg, 0.50 mmole) in 10 ml of dichloromethane was stirred for 3 hours at room temperature. Reaction mixture was neutralized by adding a saturated sodium hydrogen carbonate solution (10 ml), and then stirred at 0° for 10 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give **7a** (49 mg, 21 %) as an oil; R_f 0.65 (ethyl acetate-hexane, 1:1); ir (neat) 2962, 2928, 1681, 1620, 1391, 1268 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.16 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.75 (s, 2H, S-CH_2), 3.61 (s, 2H, H-6), 2.70 (s, 2H, H-8), 2.43 (s, 3H, CH_3), 1.25 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.98 (s, 6H, (CH_3)$_2$); ^{13}C nmr (deuteriochloroform): δ 169.7 (*C*O), 159.9 (*C*S), 156.1, 151.8, 117.4, 62.6, 61.2 ($CO_2CH_2CH_3$), 40.3, 31.8, 30.7, 26.9 ((*C*H$_3$)$_2$), 14.2 ($CO_2CH_2CH_3$), 13.7 (*C*H$_3$); ms: m/z 296 (M^+, 54), 251 (63), 223 (100); high resolution ms: m/z 296.1176 (M^+, $C_{14}H_{20}N_2O_3S$ requires 296.1195).

Ethyl 2-[(2-methyl-7,8-dihydro-6*H*-azepino[3,4-*d*][1,3]oxazol-4-yl)sulfanyl]acetate (**7b**).

The procedure to prepare **7b** was the same as for the preparation of **7a** starting with 140 mg (0.77 mmole) of **6b** and 153 mg (0.50 mmole) of ethyl bromoacetate. Compound **7b** was obtained as a yellowish solid (dichloromethane-hexane) in 78% yield; mp 192-193°; ^1H nmr (deuteriochloroform): δ 4.19 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.75 (s, 2H, S-CH_2), 3.84 (m, 2H, H-6), 2.90 (t, J = 6.9 Hz, 2H, H-8), 1.89 (m, 2H, H-7), 2.45 (s, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C nmr (deuteriochloroform): δ 169.6 (*C*O), 159.8 (*C*S), 156.4, 153.1, 130.8, 61.2 ($CO_2CH_2CH_3$), 52.3, 31.9, 26.5, 22.5, 14.2 ($CO_2CH_2CH_3$), 13.7 (*C*H$_3$); ms: m/z 268 (M^+, 35), 222 (100), 195 (77), 179 (19), 149 (25), 122 (31); high resolution ms: m/z 268.0863 (M^+, $C_{12}H_{16}N_2O_3S$ requires 268.0882).

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