SYNTHESIS OF NEW RACEMIC BICYCLIC γ-AND δ-LACTAMS BASED ON TWO-FOLD INTRAMOLECULAR CYCLIZATION

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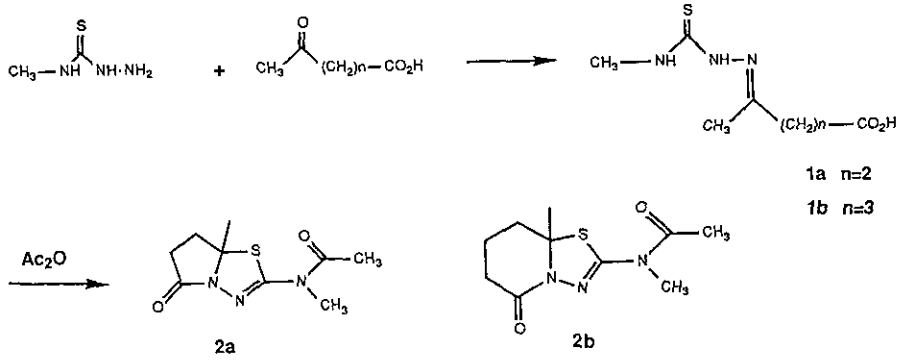
Abstract - Syntheses of new racemic γ- and δ-lactams have been achieved via a novel two-fold intramolecular cyclization.

In the last few years considerable effort has been devoted to the synthesis of stereochemically well defined γ-lactam analogues related to the penicillins[1] as well as some racemic γ-lactam analogues of both the penems[2] and carbapenems.[3] Bicyclic pyrazolidinones were also synthesized and several of these compounds exhibited broad spectrum in vitro antibacterial activity.[4,5] A recent independent paper by Taylor[6] reported the isolation of 3-(4-methoxyphenyl)-5-methyl-4-thia-1,2-diazabicyclo[3.3.0] oct-2-en-8-one, and 7-thia-1,9-diazabicyclo[4.3.0] nonenone. This prompts us to report our results concerning the synthesis of **2a**, **2b** and **5a**, **5b**.

Thus, 4-methyl-3-thiosemicarbazone of 3-acetylpropionic acid (**1a**), obtained from 4-methyl-3-thiosemicarbazide and 3-acetylpropionic acid was allowed to react in acetic anhydride to afford **2a** in 32.1% yield as outlined in Scheme 1.



1a n=2
1b n=3

2a **2b**

Scheme 1

The structure assigned to **1a** was confirmed by X-ray diffraction analysis. The ORTEP plot is shown in Figure 1.

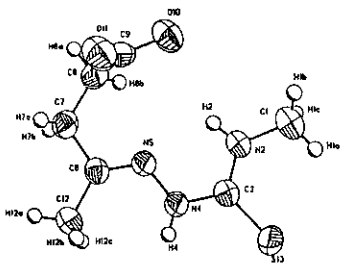
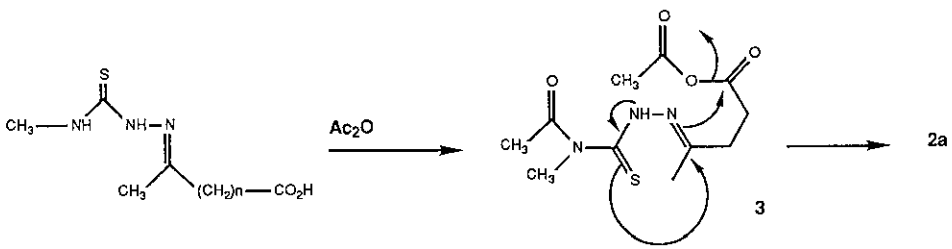


Figure 1. ORTEP plot of 1a with the numbering scheme used in the crystallographic study.

We surmise that the reaction of methyl thiosemicarbazone and acetic anhydride proceeds via the formation of the mixed anhydride **3**, followed by a novel intramolecular bis-annulation with the expulsion of an acetate ion as shown in Scheme 2.[7]



Scheme 2

The structural dimensions of **2a** and **2b** have been ascertained by means of X-ray crystallography (Figure 2). Both compounds were tested for antibiotic activity and were shown to be inactive.

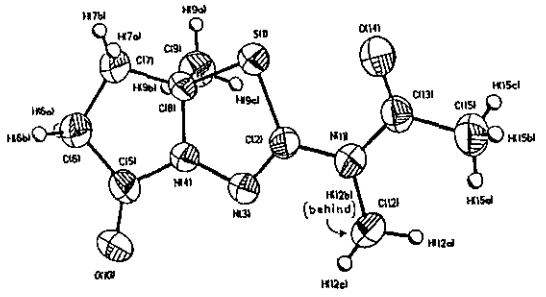
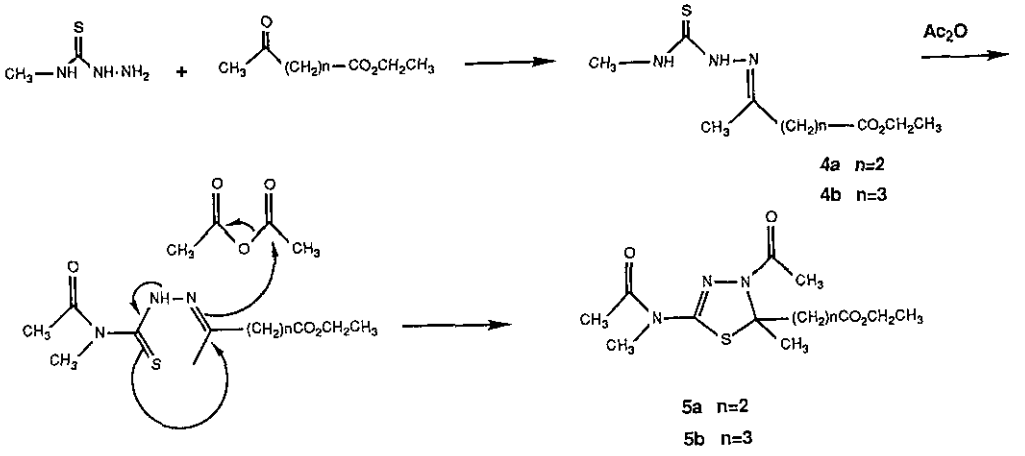


Figure 2. ORTEP plot of 2a with the numbering scheme used in the crystallographic study.

In contrast to **1a** and **1b**, formation of **2a** and **2b** was not observed when **4a** and **4b**, obtained from 4-methyl-3-thiosemicarbazide and ethyl 3-acetylpropionate and ethyl 4-acetylbutyrate, were reacted with acetic anhydride. Instead, **5a** and **5b** were obtained in 72.1% and 39.4% yields respectively. This suggests that a different reaction path has ensued, and the possible mechanism for this reaction is shown in Scheme 3.[7]



Scheme 3

The structure assigned to **4a** was also secured by X-ray diffraction analysis (Figure 3).

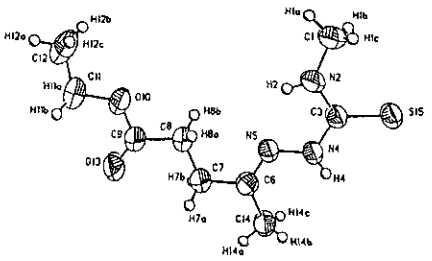


Figure 3. ORTEP plot of 4a with the numbering scheme used in the crystallographic study.

These results provide a novel synthetic approach to compounds **2a** and **2b** as depicted in Scheme 1. The success and expedience of this reaction constitute a new and useful γ - and δ -lactam synthesis which could be well suited for the preparation of compounds of future interests.

EXPERIMENTAL

Melting points were taken on Thomas Hoover capillary melting point apparatus and were uncorrected. ^{1}H-Nmr and ^{13}C-nmr spectra were determined with Jeol FX90Q and GE QE-300 spectrometers using tetramethylsilane as the internal reference. Mass spectra were obtained with a CEC 21-110 mass spectrometer.

4-[[(Methylamino)thioxomethyl]hydrazono]pentanoic acid (1a).

To a mixture of 4-methyl-3-thiosemicarbazide (42 g, 0.4 mole) in toluene (250 ml) was added a solution containing 3-acetylpropionic acid (46.4 g, 0.4 mole) and toluene (150 ml). The reaction mixture was refluxed for 2 h, cooled, filtered, and washed with toluene. The product was slurried into hot acetone (100 ml) to give **1a** (56 g, 69%), mp 167-170.5°C. ^{1}H-Nmr (δ,300 MHz, $CDCl_3$): 1.90 (s, 3H,C-CH_3); protons of the two methylene groups occur as a group of multiplets in the range of 2.55-2.65, 3.15 (d, 3H, J=6H_Z, N-CH_3), 7.75 (br s, 1H, $NHCH_3$), 8.83 (s, 1H,N-NH). ^{13}C-Nmr (300 MH_Z) exhibits three sets of sp^2 carbons, δ , 151.88, 174.45, and 178.69. $M^{+\cdot}$ 203. Anal. Calcd for $C_7H_{13}N_3O_2S$: C, 41.36; H, 6.45; N,20.67. Found: C, 41,18; H, 6.46; N, 20.61.

5-[[(Methylamino)thioxomethyl]hydrazono]hexanoic acid (1b).

White solid, 66.6%, mp 130.5-131.5°C. ^{1}H-Nmr (δ, 300 MH_Z, $CDCl_3$): 1.90 (s, 3H, C-CH_3); protons of the three methylene groups occur as a group of multiplets in the range of 1.8-2.4, 3.20 (d, 3H, J=6H_Z, N-CH_3), 7.65 (br s, 1H, $NHCH_3$), 8.65 (s, 1H, NH). $M^{+\cdot}$ 217. Anal. Calcd for $C_8H_{15}N_3O_2S$: C, 44.22; H, 6.96; N,19.34. Found: C, 43.96; H, 6.71; N, 19.31.

X-ray Crystallographic Data (1a)

Compound **1a** crystallized in the space group $P2_1/n$, Z=4, with unit cell dimensions of a=9.389A°, C=13.403A°; beta=107.190. The calculated density was 1.326 g cm^{-3}. A total of 1579 unique reflections with 2 [theta] less than 116.0 were measured on an automated four circle diffractometer using monochromatic copper radiation. The structure was solved using the Direct Methods routine SOLV of the SHELXTL program and was refined by the least square method with anisotropic temperature factors for all atoms except hydrogen. The final R- factor was 0.0627 for 1205 observed reflections.

N-Methyl-N-(5,6,7,7a-tetrahydro-7a-methyl-5-oxopyrrolo(2,1-b)-1,3,4-thiadiazol-2-yl)acetamide (2a).

To a stirred solution of acetic anhydride (100 ml) was added **1a** (10 g, 0.049 mole), and the reaction mixture was heated at 65°C for 72 h. Acetic anhydride was removed in vacuo, and the resulting oil was dissolved in methylene chloride (100 ml) which was washed successively with water, saturated sodium carbonate and water. The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo to afford **2a** (3.6 g, 32.1%), mp 165-168°C. ^{1}H-Nmr (δ, 90 MH_Z, $CDCl_3$): 1.64 (s, 3H, C-CH_3), 2.40 (s, 3H, $COCH_3$), 2.50 (m, 2H, CH_2), 2.75 (m, 2H, $COCH_2$), 3.70 (s, 3H, N-CH_3). $M^{+\cdot}$ 227. Anal. Calcd for $C_9H_{13}N_3O_2S$: C, 47.56; H, 5.77; N, 18.49. Found: C, 47.80; H, 5.68; N, 18.29.

N-Methyl-N-(6,7,8,8a-tetrahydro-8a-methyl-5-oxo-5H-1,3,4-thiadiazolo(3,2-a)pyridin-2-yl)acetamide (2b).

White solid, 33%, mp 129-132°C. ^{1}H-Nmr (δ, 90 MH_Z, $CDCl_3$): 1.70 (s, 3H, C-CH_3), protons of the three methylene groups occur as a group of poorly resolved resonances in

the range of 2.0-2.5, 2.30 (s, 3H, $COCH_3$), 3.60 (s, 3H, N-CH_3). $M^{+\cdot}$ 241. Anal. Calcd for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.63; H, 6.29; N, 17.23.

X-ray Crystallographic Data (2a).

Compound **2a** crystallized from ethanol as yellow prisms in the space group $P2_1/c$, Z=4, with unit cell having dimension a=9.172(2)A°; b=12.955(4)A°; c=9.820(s)A°; beta=113.94(2)°. The calculated density was 1.415 g cm^{-3}. A total of 1643 unique reflections with 2 [theta] less than 116.0° were measured on an automated four-circle diffractometer using monochromatic copper radiation. The position of the atoms were obtained by interpretation of an E-map phased by the direct methods routine SOLV of the SHELXTL program. The structure was refined by the least square method with anisotropic temperature factors for all atoms except hydrogen which were included at calculated positions. The final R-factor was 0.0641 for 1353 observed reflections.

4-[[(Methylamino)thioxomethyl]hydrazono]pentanoic acid ethyl ester (4a).

To a mixture of 4-methyl-3-thiosemicarbazide (32 g, 0.3 mole) in toluene (275 ml) was added a solution containing ethyl 3-acetylproprinate (43.2 g, 0.3 mole) and toluene (25 ml). The reaction mixture was refluxed for 2 h, cooled and filtered. The product was recrystallized from hexane and dried **in vacuo** to give **4a** (39.4 g, 56.3%), mp 90-91°C. ^{1}H-Nmr (δ, 300 MH_Z, $CDCl_3$): 1.25 (t, 3H, J=7H_Z, CH_3) 1.90 (s, 3H, C-CH_3), protons of the two methylene groups occur as a group of multiplets in the range of 2.5-2.6, 3.25 (d, 3H, J=6 H_Z, N-CH_3), 4.20 (q, 2H, J=7H_Z, CH_2), 7.70 (br s, 1H, NH), 8.80 (s, 1H N-NH). ^{13}C-Nmr (300 MH_Z) exhibits three sets of sp^2 carbons, δ, 149.04, 173.15 and 179.13. $M^{+\cdot}$ 231. Anal. Calcd for $C_9H_{17}N_3O_2S$: C, 46.75; H, 7.35; N, 18.78. Found: C, 46.44; H, 7.26; N, 18.45.

5-[[(Methylamino)thioxomethyl]hydrazono]hexanoic acid ethyl ester (4b).

White solid, 31%, mp 64-65°C. ^{1}H-Nmr (δ, 90 MH_Z, $CDCl_3$): 1.25 (t, 3H, J=7H_Z, CH_3), 1.90 (s, 3H, C-CH_3), protons of the three methylene groups occur as a group of multiplets in the range of 1.9-2.3, 3.20 (d,3H, J=6H_Z, N-CH_3), 4.10 (q, 2H, J=7H_Z, CH_2). $M^{+\cdot}$ 245.

Anal. Calcd for $C_{10}H_{19}N_3O_2S$: C, 48.96; H, 7.81; N, 17.13. Found: C, 48.80; H, 7.68; N, 16.88.

X-ray Crystallographic Data (4a).

Compound **4a** crystallized in the space group P^1Bar, Z=2, with unit cell dimensions a=6.892A°, b=9.102A°, c=11.251A°, beta=87.610. The calculated density was 1.254 g cm^{-3}. A total of 1766 unique reflections with 2 [theta] less than 116.0 were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved using the Direct Methods routine SOLV of the SHELXTL program and was refined by the least square method with anisotropic temperature factors for all atoms except hydrogen. The final R- factor was 0.0563 for 1226 observed reflections.

3-Acetyl-5-(acetylmethylamino)-2,3-dihydro-2-methyl-1,3,4-thiadiazole-2-propanoic acid ethyl ester (5a).

To a stirred solution of acetic anhydride (60 ml) was added **4a** (6.0 g, 0.026 mole), and the reaction mixture was heated at 55°C for 72 h. Acetic anhydride was removed **in vacuo**, and the resulting oil was dissolved in methylene chloride (100 ml) which was washed successively with water, saturated sodium bicarbonate and water. The organic layer was dried over magnesium sulfate, and the solvent was removed **in vacuo** to give **5a** as an oil (5.9 g, 72%). ^{1}H-Nmr (δ, 300 MH_z, $CDCl_3$): 1.25 (t, 3H, J=7H_z, CH_3), 1.95 (s, 3H, C-CH_3), protons of the two $COCH_3$ groups occur as two singlets in the range of 2.2 and 2.3, protons of the two methylene groups occur as a group of multiplets in the range of 2.2-2.7, 3.40 (s, 3H, N-CH_3), 4.10 (q, 2H, J=7H_z, CH_2). $M^{+\cdot}$ 315. Anal. Calcd for $C_{13}H_{21}N_3O_4S$: C, 49.51; H, 6.71; N, 13.32. Found: C, 49.32; H, 6.97; N, 13.12.

3-Acetyl-5-(acetylmethylamino)-2,3-dihydro-2-methyl-1,3,4-thiadiazole-2-butanoic acid ethyl ester (5b).

Oil, 39.4%. ^{1}H-Nmr (δ, 90 MH_z, $CDCl_3$): 1.25 (t, 3H, J=7H_z, CH_3), 1.95 (s, 3H, C-CH_3), protons of the two $COCH_3$ groups occur as two singlets in the range of 2.2 and 2.3. protons of the three methylene groups occur as a group of multiplets in the range of

1.9-2.3, 3.40 (s, 3H, N-CH_3), 4.10 (q, 2H, J=7H_Z, CH_2). $M^{+\cdot}$ 329. Anal. Calcd for $C_{14}H_{23}N_3O_4S$: C, 51.05; H, 7.04; N, 12.76. Found: C, 51.12; H, 7.04; N, 12.66.

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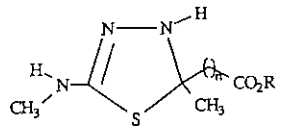
REFERENCES AND NOTES

1. J. E. Baldwin, M. F. Chan, G. Gallacher, P. Monk, and K. Prout, J. Chem. Soc., Chem. Commun., 1983, 250.
2. D. B. Boyd, T. K. Elzey, L. D. Hatfield, M. D. Kinnick, and J. M. Morin, Jr., Tetrahedron Lett., 1986, 27, 3453.
3. D. B. Boyd, B. J. Foster, L. D. Hatfield, W. J. Hornback, N. D. Jones, J. E. Munroe, and J. K. Swartzendruber, Tetrahedron Lett., 1986, 27, 3457.
4. L. N. Jungheim, S. K. Sigmund, and J. W. Fisher, Tetrahedron Lett., 1987, 28, 285.
5. L. N. Jungheim, S. K. Sigmund, N. D. Jones, and J. K. Swartzendruber, Tetrahedron Lett., 28, 289.
6. D. M. Evans, L. Hill and D. R. Taylor, J. Chem. Soc. Perkin Trans. 1, 1986, 1499.
7. Our experimental results led us to conclude that the thiosemicarbazones of both the keto-acids and its corresponding esters prefer to exist as the acylic tautomer as opposed to the cyclic tautomer. However, as the referee pointed out, the cyclic intermediates **6a** and **6b** cannot be ruled out in this reaction.



6a R=H
6b R=CH_2CH_3

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