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# A New, Highly Efficient, and Simple Procedure for the Construction of Medium-Sized Nitrogen Heterocyclic Ring System

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**Synopsis.** Two types of sulfur- and nitrogen-containing heterocycles have been synthesized from a tetrahydro-4-oxothiophene derivative.

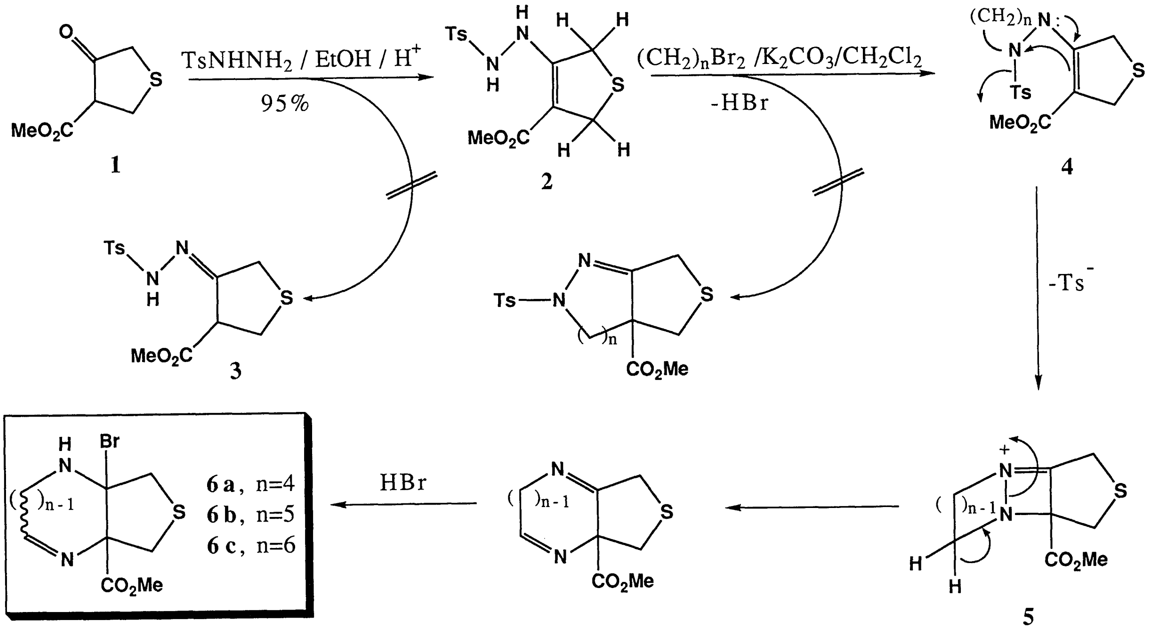
In the course of study towards the synthesis of various types of new 1,2,3-thiadiazole derivatives, we discovered the utility of a new reagent for the preparation of medium-sized nitrogen heterocycles. Thus, we wish to report on the synthesis of 8, 9, and 10-membered nitrogen heterocycles (**6**) from the substituted hydrazide (**2**) as well as a novel heterocyclic ring system, thieno[3,2-*d*][1,2,3]thiadiazole derivative (**7**). The procedure described herein is concerned with the formation of substituted 1,2-diazacycloalkanes via the reaction of **2** with $\alpha,\omega$-dibromoalkanes [$(CH_2)_nBr_2$; $n$=4,5,6]. Further rearrangement followed by ring enlargement leads to the medium-sized nitrogen heterocycles. The new procedure has generality and is completely different from previously reported methods.[1–8]

## Results and Discussion

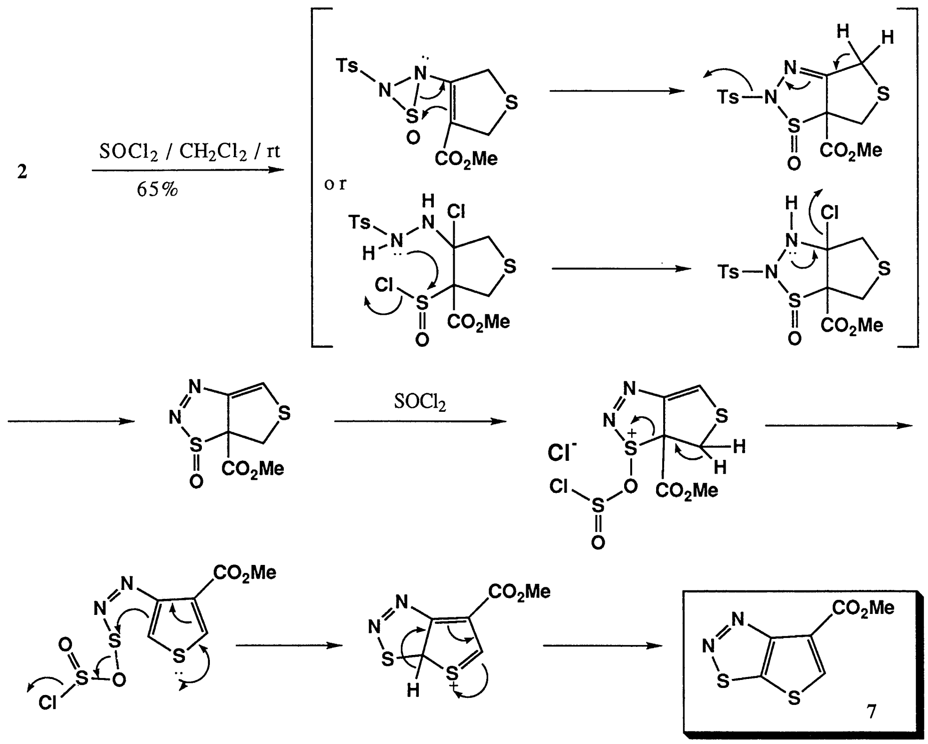
Methyl tetrahydro-4-oxothiophene-3-carboxylate (**1**),[9–11] was condensed with *p*-toluenesulfonohydrazide in the presence of concd HCl in ethanol, which afforded **2** instead of its tautomer, a hydrazone derivative (**3**). Condensation of **2** with $\alpha,\omega$-dibromoalkanes in the presence of potassium carbonate in refluxing dichloromethane afforded the medium-sized nitrogen heterocyclic ring systems (**6a**—**c**). In the probable reaction sequence depicted in Scheme 1, the crucial step is the formation of a 1,2-diazacycloalkanes derivative (**4**). The step is then followed by detosylation to form a new C–N bond, which leads to an intermediate **5**. The ring enlargement of **5**, followed by the addition of HBr on the ring junction, results in the formation of medium-sized nitrogen heterocycles **6**.

$^{1}$H and $^{13}$C NMR spectroscopies showed that **6a**—**c** are 70:30 mixtures of the trans- and cis-isomers with respect to the HC=N moiety. We attempted to separate the diastereomers by various methods, all of which were unsuccessful.

The cis- and trans-configurational assignment in **6** was based mainly on $^{1}$H NMR studies: the difference NOE spectrum of **6b** exerts a strong (16.2%) signal from the olefinic proton in the higher-ratio isomer when the signal from the NH proton in the higher-ratio isomer was irradiated and vice versa (14.2%). On the other hand, the irradiation at the signal from either



Scheme 1.



Scheme 2.

the olefinic or NH proton in the lower-ratio isomer did not affect the intensity of the signal from the corresponding proton, respectively. The observation suggests that the higher-ratio isomer has the trans-configuration in good agreement with the structure assigned by normal $^1$H NMR spectroscopy.[12] The lower-ratio isomer is then assigned as the cis-isomer. A homonuclear 2D NOESY experiment confirmed this conclusion demonstrating a strong NOE cross peaks for H-6 to NH. The homonuclear 2D COSY spectrum of **6b** exerts strong couplings of signals from H-5 to that from H-6, H-8 to H-9, and H-12 to NH. The other compunds **6a** and **6c** gave similar results from the NMR spectroscopy.

When the substituted hydrazide derivative **2** was treated with excess thionyl chloride in dichloromethane at room temperature for 8 h, methyl thieno [3,2-*d*][1,2,3]thiadiazole-6-carboxylate (**7**) was afforded in 65% yield. Although the synthesis of the same heterocyclic system was reported by Paulmier,[13] our synthesis described herein is completely different in approach from the previous one and gives a better yield.[14] The formation of **7** is described in Scheme 2 with a plausible mechanism.

In summary, the method may be applicable to vinylic hydrazides of the type **2** and one can achieve the system of medium-sized heterocycles starting from various kinds of cyclic 1,3-ketoester derivatives.

## Experimental

**Instruments.** Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were taken on a Perkin-Elmer, model 1720, FT-IR spectrometer. The $^1$H, $^{13}$C NMR, 2D COSY, NOEDS, and NOESY spectra were obtained on Varian VXR 200 and JEOL 400 MHz instruments. Mass spectra were recorded on JEOL JMS-DX 300. Elemental analyses were obtained on Yanaco MT-3 elemental analyzer.

**Methyl 2,5-Dihydro-4-(*N′*-tosylhydrazino)thiophene-3-carboxylate (2).** Methyl tetrahydro-4-oxothiophene-3-carboxylate (**1**) (1.60 g, 0.01 mol) and *p*-toluenesulfonohydrazide (1.862 g, 0.01 mol) were dissolved in absolute ethanol (50 cm$^3$) with a few drops of concd HCl. The reaction mixture was stirred at room temperature for 30 min and the solid precipitated out. The solid was filtered and dried. The crude product was recrystallized from ethanol to give analytically pure title compound **2** as colorless crystalline solid (3.45 g, 95%), mp 169—171 °C. This compound showed a couple of AB-quartets for the $CH_2SCH_2$ protons at $\delta$=3.96 and 3.83 in $CDCl_3$ indicating that these methylene protons have no vicinal protons to couple with. These signals are largely affected by the solvent polarity supporting that they are indeed AB-quartets.

IR (KBr) $\nu_{max}$ 3209 and 1656 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.46 (s, 3H), 3.68 (s, 3H), 3.81 (ABq, 2H, *J*=3.2 Hz), 3.97 (ABq, 2H, *J*=3.2 Hz), 6.37 (brs, 1H), 7.36 (d, 2H, *J*=8 Hz), 7.73 (d, 2H, *J*=8.6 Hz), and 8.64 (brs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$=21.73, 34.77, 36.33, 51.24, 97.42, 128.16, 130.13, 132.86, 145.35, 160.65, and 167.20; MS (70 eV, EI) *m/z* (rel intensity) 328 (M$^+$, 29.6). Anal. Found: C, 47.53; H, 4.83; N, 8.61%. Calcd for $C_{13}H_{16}O_4N_2S_2$: C, 47.56; H, 4.88; N, 8.54%.

**General Procedure for the Reaction of 2 with $\alpha,\omega$-Dibromoalkanes.** A suspension of **2** (0.656 g, 2 mmol) and anhydrous potassium carbonate (1 g) in dichloromethane was stirred under nitrogen at room temperature. To the suspension, an $\alpha,\omega$-dibromoalkane (3 mmol) was added dropwise and the mixture was initially stirred at room temperature then refluxed for 18 h. The reaction mixture was filtered and the filtrate was washed several times with water. The solvent was removed in vacuo and the reidue was purified by column chromatography on silica gel and eluted with hexane–ethyl acetate (95:5) mixture affording the medium-sized nitrogen heterocycle **6**.

**Methyl 8-Bromo-10-thia-2,7-diazabicyclo[6.3.0]undec-2-ene-1-carboxylate (6a):** Mp 58—60 °C; 48% yield. IR (KBr) $\nu_{max}$ 1618, 1666, and 3350 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.08 (m, 2H), 2.42 (q, 2H, $J$=7.4 Hz), 3.44 (trans) and 3.46 (cis) (t, 2H, $J$=6.4 Hz), 3.70 (trans) and 3.74 (cis) (s, 3H), 3.84 (ABq 2H, $J$=3.1 Hz), 4.14 (ABq, 2H, $J$=3.1 Hz), 6.49 (cis) and 7.14 (trans) (t, 1H, $J$=5.0 Hz), and 10.52 (trans) and 10.72 (cis) (bs, 1H); MS (70 eV, EI) $m/z$ (rel intensity) 306 (M$^+$, 12.9). Anal. Found: C, 39.70; H, 4.90; N, 8.51%. Calcd for $C_{10}H_{15}BrN_2O_2S$: C, 39.08; H, 4.88; N, 9.12%.

**Methyl 9-Bromo-11-thia-2,8-diazabicyclo[7.3.0]dodec-2-ene-1-carboxylate (6b):** Mp 55—57 °C; 54% yield. IR (KBr) $\nu_{max}$ 1624, 1679, and 3435 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.67 (m, 2H), 1.91 (m, 2H), 2.29 (m, 2H), 3.42 (trans) and 3.44 (cis) (t, 2H, $J$=6.4 Hz), 3.72 (cis) and 3.74 (trans) (s, 3H), 3.86 (ABq, 2H, $J$=3.0 Hz), 4.15 (ABq, 2H, $J$=3.0 Hz), 6.51 (cis) and 7.13 (trans) (t, 1H, $J$=5.2 Hz), and 10.51 (trans) and 10.72 (cis) (bs, 1H); MS (70 eV, EI) $m/z$ (rel intensity) 320 (M$^+$, 14.6). Anal. Found: C, 41.45; H, 5.30; N, 8.25%. Calcd for $C_{11}H_{17}BrN_2O_2S$: C, 41.12; H, 5.29; N, 8.72%.

**Methyl 10-Bromo-12-thia-2,9-diazabicyclo[8.3.0]tridec-2-ene-1-carboxylate (6c):** Mp 38—39 °C: 45% yield. IR (KBr) $\nu_{max}$ 1612, 1667, and 3360 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.49 (m, 2H), 1.58 (m, 2H), 1.86 (m, 2H), 2.25 (m, 2H), 3.39 (trans) and 3.40 (cis) (t, 2H, $J$=3.3 Hz), 3.70 (trans) and 3.73 (cis) (s, 3H), 3.85 (ABq, 2H, $J$=3.3 Hz), 4.15 (ABq, 2H, $J$=3.3 Hz), 6.50 (cis) and 7.11 (trans) (t, 1H, $J$=5.2 Hz), and 10.48 (trans) and 10.68 (cis) (bs, 1H); MS (70 eV, EI) $m/z$ (rel intensity) 334 (M$^+$, 59.6). Anal. Found: C, 43.22; H, 5.78; N, 8.41%. Calcd for $C_{12}H_{19}BrN_2O_2S$: C, 42.99; H, 5.67; N, 8.35%.

**Methyl Thieno[3,2-*d*][1,2,3]thiadiazole-6-carboxylate (7).** To a solution of **2** (3.28 g, 0.01 mol) in dry dichloromethane (100 cm$^3$) was added thionyl chloride (21.9 cm$^3$, 0.3 mol) dropwise, and the resulted mixture was stirred at room temperature for 8 h. Excess $SOCl_2$ was evaporated in vacuo and residual traces were removed by azeotropic vacuum distillation with benzene. The resulted residue was purified by column chromatography on silica gel by using 10% ethyl acetate–hexane mixture as an eluent. Recrystallization of the material from ethanol afforded pure sample of **7** (1.326 g, 65% yield) as orange red crystals, mp 104—106 °C; IR (KBr) $\nu_{max}$ 1694 cm$^{-1}$; $^1$H NMR ($CDCl^3$) $\delta$=4.05 (s, 3H) and 8.53 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$=52.68, 122.74, 142.35, 146.62, 161.15, and 166.42; MS (70 eV, EI) $m/z$ 200 (M$^+$, 100). Anal. Found: C, 36.11; H, 2.02; N, 14.16%. Calcd for $C_6H_4O_2N_2S_2$: C, 36.00; H, 2.00; N, 14.00%.

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