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Olefin Cyclization Initiated by α-Thiocarbocation: A Novel Route to Pyrrolizidine Alkaloids

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Ethyl [1-(methylsulfinyl)acetyl-2-pyrrolidinylidene]acetate (**3**), on treatment with trifluoroacetic anhydride in dichloromethane at 0 °C and then 10—20 °C, gave ethyl 1-aza-3-methylthio-2-oxobicyclo[3.3.0]oct-4-ene-4-carboxylate (**6**), which was converted into ethyl (4*RS*,5*SR*)-1-aza-2-oxobicyclo[3.3.0]octane-4-carboxylate (**7**) by reduction with Raney nickel.

Keywords——pyrrolizidine alkaloid; isoretronecanol; trachelanthamidine; olefin cyclization; Pummerer reaction; thionium ion; alpha-thiocarbocation; ethyl 2-pyrrolidinylideneacetate

In a series of papers,[1] we have shown that the Pummerer reaction intermediates, $MeS\overset{+}{C}HCOR$, derived from α-acylsulfoxides, $MeS(O)CH_2COR$, can act as effective initiators for olefin cyclization. In this paper we wish to describe a novel route to some pyrrolizidine alkaloids which involves the cyclization of the *N*-[α-(methylsulfinyl)acetyl]-enaminoester **3** under the Pummerer reaction conditions as a key step.

The enaminoester **3** was synthesized by *N*-acylation of the readily available enaminoester **1**[2] with α-(methylthio)acetic anhydride and pyridine, followed by oxidation of the resultant sulfide **2** with sodium metaperiodate.

Heating of a benzene solution of the sulfoxide **3** in the presence of *p*-toluenesulfonic acid resulted in the formation of polymeric material. However, treatment of **3** with trifluoroacetic anhydride in dichloromethane at 0 °C and then 10—20 °C afforded the expected pyr-

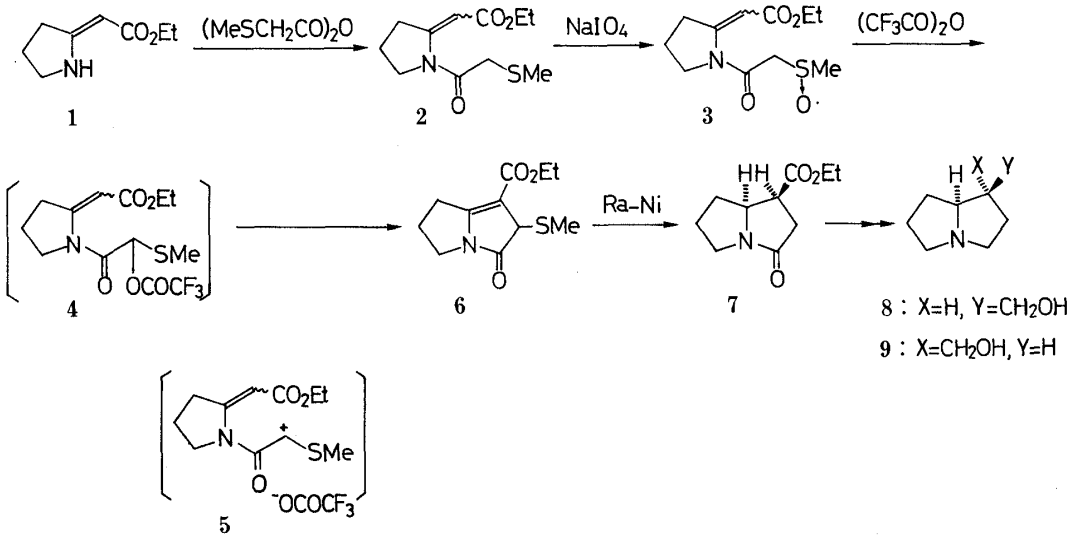

Chart 1

rolizidinone ester **6** in 31% yield; the structure was assigned on the basis of spectroscopic evidence (see Experimental). When the reaction was carried out without warming to 10—20 °C, only the normal Pummerer reaction product **4** was detected in the crude reaction mixture by thin layer chromatography and ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy [δ 6.10 (1H, s, COCH(OCOCF$_3$)SMe]. The formation of **6**, therefore, may be viewed as proceeding *via* the trifluoroacetate **4**, which cyclizes to **6** either in a stepwise manner involving a carbonium ion intermediate **5** or by a concerted S_N2-like mechanism. Reduction of **6** with Raney nickel gave the pyrrolizidinone ester **7** in 66% yield. The conversion of **7** into (±)-isoretronecanol (**8**) and (±)-trachelanthamidine (**9**) has already been described in the literature.[3]

Experimental[4]

Ethyl [1-(Methylthio)acetyl-2-pyrrolidinylidene]acetate (2)——A solution of **1**[2] (2.25 g, 14.5 mmol) in α-(methylthio)acetic anhydride[5] (11.5 g, 59 mmol) and pyridine (1.35 ml, 16.7 mmol) was heated at 120 °C for 1 h. The reaction mixture was poured into water (30 ml) and extracted with benzene. The organic layer was washed successively with 10% Na_2CO_3 solution, 10% HCl, and brine, and then dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (benzene–ethyl acetate, 10 : 1). The first eluate gave **2** (1.53 g, 43%): mp 44—44.5 °C (from *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1615. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, OCH_2CH_3), 1.6—2.4 (2H, m, ring 4-H), 2.19 (3H, s, SCH_3), 3.18 (2H, dt, J=7, 2 Hz, ring 3-H), 3.29 (2H, s, SCH_2), 3.84 (2H, t, J=7 Hz, ring 5-H), 4.14 (2H, q, J=7 Hz, OCH_2CH_3), 6.88 (1H, t, J=2 Hz, C=CH). *Anal.* Calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76. Found: C, 54.15; H, 7.26; N, 6.01. The second eluate gave the *C*-acylated product, ethyl 4-methylthio-3-oxo-2-(2-pyrrolidinylidene)butanoate (0.22 g, 6%), as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1600, 1550. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, OCH_2CH_3), 1.7—2.4 (2H, m, ring 4-H), 2.12 (3H, s, SCH_3), 3.18 (2H, br t, J=7 Hz, ring 3-H), 3.67 (2H, t, J=8 Hz, ring 5-H), 3.84 (2H, s, SCH_2), 4.21 (2H, q, J=7 Hz, OCH_2CH_3), 11.6 (1H, br, NH). Exact MS *m/z*: Calcd for $C_{11}H_{17}NO_3S$: 243.0928. Found: 243.0959.

Ethyl [1-(Methylsulfinyl)acetyl-2-pyrrolidinylidene]acetate (3)——A solution of sodium metaperiodate (421 mg, 2.2 mmol) in water (5 ml) was added dropwise to an ice-cooled solution of **2** (487 mg, 2.0 mmol) in methanol (10 ml), and stirring was continued at room temperature for 10 h. The precipitated inorganic material was removed by filtration and the filtrate was extracted with $CHCl_3$, then the organic layer was dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (benzene–ethyl acetate, 1 : 1) to give **3** (462 mg, 89%): mp 147.5—148.5 °C (from benzene–*n*–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1615. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 1.6—2.4 (2H, m, ring 4-H), 2.78 (3H, s, SCH_3), 3.18 (2H, dt, J=7, 2 Hz, ring 3-H), 3.87 (2H, t, J=7 Hz, ring 5-H), 3.91 (2H, s, SCH_2), 4.12 (2H, q, J=7 Hz, OCH_2CH_3), 6.87 (1H, t, J=2 Hz, C=CH). *Anal.* Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.73; H, 6.60; N, 5.57.

Ethyl 1-Aza-3-methylthio-2-oxobicyclo[3.3.0]oct-4-ene-4-carboxylate (6)——Trifluoroacetic anhydride (149 mg, 0.71 mmol) was added to a solution of **3** (184 mg, 0.71 mmol) in CH_2Cl_2 (10 ml) at 0 °C and the mixture was stirred at the same temperature for 30 min, and then at 10—20 °C for 2.5 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (benzene–ethyl acetate, 10 : 1) to give **6** (53 mg, 31%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 2.1—2.7 (2H, m, 7-H), 2.19 (3H, s, SCH_3), 2.7—3.2 (2H, m, 6-H), 3.59 (2H, t, J=7 Hz, 8-H), 4.16 (2H, q, J=7 Hz, OCH_2CH_3), 4.20 (1H, s, SCH). Exact MS *m/z*: Calcd for $C_{11}H_{15}NO_3S$: 241.0771. Found: 241.0769.

Ethyl (4*RS*,5*SR*)-1-Aza-2-oxobicyclo[3.3.0]octane-4-carboxylate (7)——A solution of **6** (50 mg, 0.21 mmol) in CH_2Cl_2 (5 ml) containing Raney nickel W-2 (1.4 g) was heated under reflux for 5 min. After removal of the Raney nickel, the solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate–benzene, 1 : 1) to give **7** (27.3 mg, 66%) as an oil, whose spectroscopic data were identical with those described in the literature.[3]

References and Notes

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4) All melting points are uncorrected. ^{1}H-NMR spectra were determined with a JNM-PMX 60 (60 MHz) spectrometer (tetramethylsilane as an internal standard). Infrared (IR) spectra were recorded with a JASCO A-100 spectrophotometer. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV.
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