Organic Chemistry

Sulfur ylides
12.* Optically active keto stabilized sulfur ylide obtained from L-proline: synthesis and study

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Optically active keto stabilized sulfur ylide was synthesized from L-proline. The reactions of the ylide with methyl acrylate and methyl vinyl ketone afforded 1,2-disubstituted cyclopropanes. In the case of acrylonitrile, a mixture of 1,2- and 1,1-disubstituted cyclopropanes was obtained. Acylation of the ylide with acetic anhydride gave twice stabilized sulfur ylide.

Key words: L-proline, keto stabilized sulfonium ylide, cyclopropanation, rearrangement, acylation.

In continuation of the studies[1—8] aimed at synthesizing sulfonium ylides from amino acids, we obtained optically active keto stabilized sulfur ylide **1** from L-proline (Scheme 1) and studied its reactions with activated olefins and acetic anhydride.

The reaction of protected L-proline **2** with $ClCO_2Me$ affords a mixed anhydride **3**, which reacts with an ethereal solution of CH_2N_2 to give diazo ketone **4** in 78% yield. Acylation of CH_2N_2 with acid chloride **5** proved to be less efficient (the yield of diazo ketone **4** was 56%). The IR spectrum of compound **4** contains an absorption band at 2140 cm^{-1} characteristic of a diazo group. The reaction of diazo ketone **4** with aqueous HBr affords α-bromomethyl ketone **6**, which reacts with Me_2S to give sulfonium salt **7** in 55% yield. Deprotonation of salt **7** with a mixture of a saturated solution of K_2CO_3 and 12.5 *M* NaOH leads to an optically active keto stabilized ylide **1** in 98% yield. In ylide **1**, the negative charge at the ylide C atom is delocalized over the carbonyl group; as a result, the absorption band of this group is shifted to longer wavelengths (1565 cm^{-1}).

We proposed a more efficient method for the synthesis of ylide **1** *via* catalytic decomposition of diazo ketone **4** with rhodium acetate in the presence of Me_2S; the yield of ylide **1** was 50%. This method makes it unnecessary to obtain bromo ketone and sulfonium salt and deprotonate the latter (the overall yield was 40%).

Ylide **1** is easily cyclopropanated with activated olefins. The reaction of ylide **1** with methyl vinyl ketone affords a 1 : 2 mixture of *cis*- and *trans*-isomers **8** in 80%

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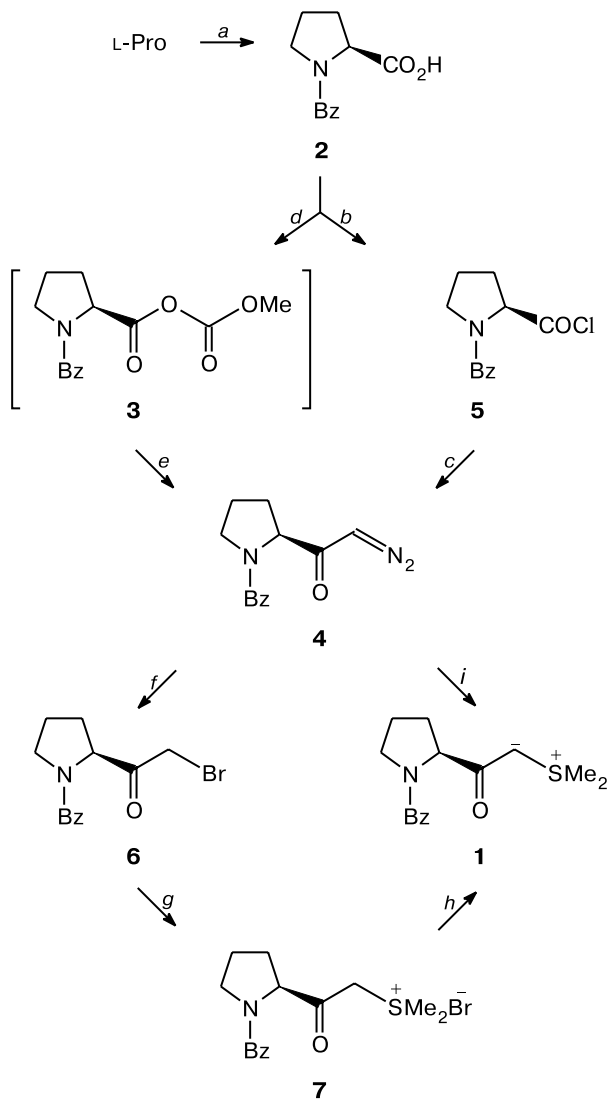
Scheme 1

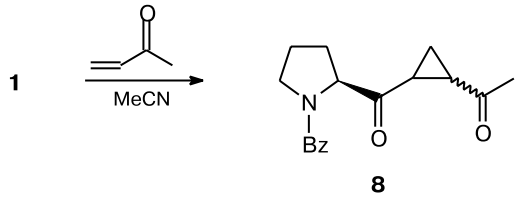


Reagents and conditions: *a*) BzCl, NaOH, ~20 °C, 75%; *b*) $(COCl)_2$/DMF, CH_2Cl_2, ~20 °C; *c*) CH_2N_2, CH_2Cl_2, −5 °C, 56%; *d*) $ClCO_2Me/Et_3N$, Et_2O, ~20 °C; *e*) CH_2N_2, Et_2O, 78%; *f*) HBr, CH_2Cl_2, ~20 °C, 74%; *g*) Me_2S, Me_2CO, ~20 °C, 55%; *h*) K_2CO_3, NaOH, $CHCl_3$, −5 °C, 98%; *i*) $Rh_2(OAc)_4$, Me_2S, CH_2Cl_2, 40 °C, 50%.

yield (Scheme 2). The ratio of the isomers was determined from the intensities of signals at δ_H 2.15 and 2.25 for the acetyl protons in the ^{1}H NMR spectrum. The higher-field signal corresponds to the *cis*-isomer, which is due to the 1,2-*syn*-interaction of the oxo group with the protons of the acetyl group.[9]

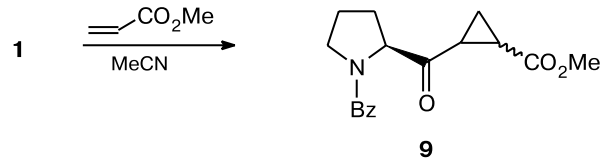
The reaction of ylide **1** with methyl acrylate in MeCN at 80 °C gave a 1 : 1 mixture of *cis*- and *trans*-isomers of methyl cyclopropanecarboxylate **9** in 80% yield (Scheme 3). The ratio of the isomers was determined

Scheme 2



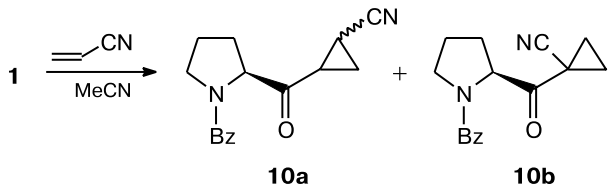
from the relative intensities of two singlets at δ_H 3.60 and 3.80 for the methoxycarbonyl protons in the ^{1}H NMR spectrum.

Scheme 3



Previously,[10] it was shown that cyclopropanation of acrylonitrile with a sulfur ylide obtained from *N*-phthaloyl-β-alanine is accompanied by rearrangement into 1,1-disubstituted cyclopropane. In the case of ylide **1**, cyclopropanation of acrylonitrile affords a 1 : 3 mixture of 1,2- (**10a**) and 1,1-disubstituted cyclopropanes (**10b**) (Scheme 4). In the ^{13}C NMR spectrum of the mixture obtained, two triplets for methylene C atoms at δ_C 21.72 and 21.61 and a singlet for the quaternary C atom at δ_C 17.42 were unambiguously assigned to the 1,1-isomer **10b**. Signals for the cyclopropane C atoms in the 1,2-isomer **10a** appear as two doublets at δ_C 24.46 and 6.98 and a triplet at δ_C 16.42. The ratio of isomers **10a** and **10b** was determined from the relative intensities of two multiplets at δ_H 3.55 (**10b**) and 3.75 (**10a**) for the CH_2N protons of the pyrrolidine ring in the ^{1}H NMR spectrum.

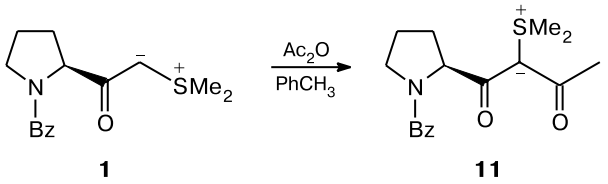
Scheme 4



Acylation of ylide **1** with acetic anhydride in toluene affords twice stabilized ylide **11** (Scheme 5). In its IR spectrum, the absorption band of the CO group bound to the ylide C atom is shifted to longer wavelengths (1580 cm^{-1}) compared to the starting ylide **1**. The ^{13}C NMR spectrum shows a signal for the ylide C atom at

δ_C 86.2. In the ^{1}H NMR spectrum, a signal at δ_H 2.35 for the acetyl group is most characteristic.

Scheme 5



1 **11**

Experimental

IR spectra were recorded on UR-20 and Specord M-80 instruments (in Vaseline oil). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) with Me_4Si as the internal standard. Specific rotation was determined on a Perkin—Elmer 241 MC polarimeter. Specific rotation is expressed in deg mL g^{-1} dm^{-1}; the concentration of solutions is expressed in g (100 mL)$^{-1}$; wavelength is 589 nm. The course of the reaction was monitored by TLC on Silufol UV-254 plates (Czech Republic); visualization under UV light or with ninhydrin. The reaction products were isolated by column chromatography on silica gel. Diethyl ether was dried over KOH and distilled. Solvents (Me_2CO, CH_2Cl_2, $CHCl_3$, and MeCN) were distilled over P_2O_5. Methyl acrylate, acrylonitrile, and methyl vinyl ketone were purified by distillation. Toluene was refluxed and distilled over sodium; Me_2S was dried over 4A molecular sieves. L-Proline (pure grade, Reanal Co.) and benzoyl chloride (pure grade, Shostka Chemical Plant) were used as purchased.

***N*-Benzoyl-L-proline (2)** was obtained in 75% yield according to the known procedure; its spectroscopic characteristics are identical with the literature data.[11]

1-Benzoyl-2-(2-diazo-1-oxoethyl)pyrrolidine (4). ***A.*** To a suspension of *N*-benzoyl-L-proline **2** (2.19 g, 10 mmol) in 90 mL of dry diethyl ether $ClCO_2Me$ (0.85 mL, 11 mmol) was added in one portion at 20 °C. The reaction mixture was stirred for 0.5 h. Triethylamine (1.4 mL, 11 mmol) was added in two portions spaced at 0.5 h, and stirring was continued for an additional 0.5 h. The precipitate of $Et_3N \cdot HCl$ that formed was filtered off. An ethereal solution of CH_2N_2 obtained from nitrosomethylurea (NMU) (2 g, 20 mmol) was added dropwise at 0 °C to the stirred filtrate. The reaction mixture was left at 0 °C for 12 h. The solvent was removed to give diazo ketone **4** (1.89 g, 78%) as a heavy light yellow oil.

B. One drop of DMF and then $(COCl)_2$ (2.5 g, 20 mmol) in 10 mL of CH_2Cl_2 were added at 0 °C to a stirred solution of *N*-benzoyl-L-proline **2** (2.19 g, 10 mmol) in 35 mL of CH_2Cl_2. The mixture was warmed to ~20 °C and stirred until gas evolution ceased. The solvent was removed. Crude 1-benzoylpyrrolidine-2-carbonyl chloride (**5**) was immediately used in the reaction with CH_2N_2. A solution of acid chloride **5** (2.38 g, 10 mmol) in 20 mL of CH_2Cl_2 was added dropwise at −5 °C to 40 mL of an ethereal solution of CH_2N_2 obtained from NMU (4 g, 40 mmol), and the reaction mixture was stirred at −5 °C for 0.5 h. The solvent was removed, and diazo ketone **4** was purified by column chromatography in chloroform—acetone (9 : 1). The yield of compound **4** was 1.37 g (56%). Found (%): C, 63.87; H, 5.63; N, 17.05. $C_{13}H_{13}N_3O_2$. Calculated (%): C, 64.19; H, 5.39; N, 17.27. IR, ν/cm^{-1}: 1705, 1776, 2140. ^{1}H NMR ($CDCl_3$), δ: 1.75—1.93, 2.05—2.31, 3.50—3.71 (all m, 2 H each, CH_2); 4.71 (t, 1 H, CH, J = 5.4 Hz); 5.61 (s, 1 H, CH); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 25.04, 28.86, 50.52, 53.05, 63.29, 127.41, 128.32, 130.36, 136.04, 170.04, 193.52.

1-Benzoyl-2-bromoacetylpyrrolidine (6). A 48% solution of HBr (10 mL) was added at 0 °C to a stirred solution of diazo ketone **4** (2.43 g, 10 mmol) in 20 mL of CH_2Cl_2. After gas evolution ceased, the reaction mixture was stirred for an additional 0.5 h. The mixture was warmed to ~20 °C and poured into 10 mL of water. The organic layer was separated, washed with 5% Na_2CO_3, and dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on SiO_2 in a short column with chloroform—acetone (9 : 1) as the eluent to give compound **6** (2.19 g, 74%) as a light yellow oil. Found (%): C, 52.57; H, 4.55; Br, 26.75; N, 4.65. $C_{13}H_{14}BrNO_2$. Calculated (%): C, 52.72; H, 4.76; Br, 26.98; N, 4.73. IR, ν/cm^{-1}: 1700, 1780. ^{1}H NMR ($CDCl_3$), δ: 1.73—1.90, 2.15—2.29, 3.45—3.61, 4.00—4.20 (all m, 2 H each, CH_2); 4.72 (t, 1 H, CH, J = 7.2 Hz); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 25.43, 29.97, 33.31, 49.92, 62.85, 126.84, 127.96, 130.20, 134.79, 169.27, 200.30.

1-Benzoyl-2-(dimethylsulfonioacetyl)pyrrolidine bromide (7). A solution of bromo ketone **6** (2.96 g, 10 mmol) and Me_2S (1.86 g, 30 mmol) in 7 mL of Me_2CO was stirred at ~20 °C in the presence of 4A molecular sieves and left for ~14 h. The salt that formed was filtered off and washed with Me_2CO to give compound **7** (1.97 g, 55%) as white crystals, m.p. 107—110 °C. Found (%): C, 50.15; H, 5.55; Br, 21.75; N, 3.65; S, 8.71. $C_{15}H_{20}BrNO_2S$. Calculated (%): C, 50.28; H, 5.63; Br, 22.31; N, 3.91; S, 8.95. IR, ν/cm^{-1}: 1615, 1690. ^{1}H NMR (CF_3COOH), δ: 1.80—2.00, 2.25—2.30 (both m, 2 H each, CH_2); 2.90, 3.00 (both s, 3 H each, SMe_2); 3.55—3.61 (m, 2 H, CH_2); 4.85 (t, 1 H, CH, J = 7.1 Hz); 5.15 (m, 2 H, CH_2); 7.20—7.50 (m, 5 H, Ar). ^{13}C NMR (CF_3COOH), δ: 25.12, 25.29, 28.67, 52.15, 53.39, 66.38, 127.68, 129.25, 129.66, 133.42, 173.43, 181.22.

1-Benzoyl-2-(dimethylsulfuranylideneacetyl)pyrrolidine (1). ***A.*** A saturated solution of K_2CO_3 (1.74 mL) and 12.5 *M* NaOH (0.3 mL) was added in one portion at 0 °C to a stirred suspension of salt **7** (1.07 g, 3 mmol) in 5 mL of $CHCl_3$. The reaction mixture was stirred for 15 min and then warmed to ~20 °C. The organic layer was separated and dried over K_2CO_3. The solvent was removed to give ylide **1** as a light yellow oil. The yield of compound **1** was 0.81 g (98%), $[\alpha]_D^{18}$ −150.4 (*c* 0.1, $CHCl_3$). Found (%): C, 65.05; H, 6.55; N, 5.15; S, 10.91. $C_{15}H_{19}NO_2S$. Calculated (%): C, 64.95; H, 6.90; N, 5.05, S, 11.56. IR, ν/cm^{-1}: 1565, 1645. ^{1}H NMR ($CDCl_3$), δ: 1.72—1.89, 2.05—2.19 (both m, 2 H each, CH_2); 2.59 (s, 6 H, SMe_2); 3.48—3.71 (m, 2 H, CH_2); 4.09 (t, 1 H, CH, J = 15 Hz); 4.50 (s, 1 H, CH); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 25.21, 28.30, 29.72, 50.43, 52.46, 66.07, 226.95, 127.71, 129.67, 137.30, 170.14, 188.19.

B. A solution of diazo ketone **4** (0.39 g, 1.6 mmol) in 7 mL of CH_2Cl_2 was added dropwise over 0.5 h to a stirred solution of Me_2S (0.5 g, 8 mmol) and $Rh_2(OAc)_4$ (0.0007 g, 0.016 mmol) in 15 mL of CH_2Cl_2. The reaction mixture was refluxed until gas evolution ceased. The course of the reaction was monitored by TLC in $CHCl_3$—Me_2CO (9 : 1); visualization with ninhydrin.

The completion of the reaction was concluded from the absence of the diazo ketone. The reaction mixture was washed with water and dried over Mg_2SO_4; the solvent was removed. The yield of ylide **1** was 0.22 g (50%).

Cyclopropanation (general procedure). An olefin (1.5 mmol) was added to a solution of ylide **1** (0.28 g, 1 mmol) in 5 mL of MeCN. The reaction mixture was refluxed for 2 h. The solvent was removed, and the residue was chromatographed on Al_2O_3 in a short column (chloroform—acetone (9 : 1) as the eluent).

2-(2-Acetylcyclopropanecarbonyl)-1-benzoylpyrrolidine (8) was obtained as a light yellow oil. The yield of compound **8** was 0.23 g (80%). Found (%): C, 71.25; H, 6.35; N, 4.33. $C_{17}H_{19}NO_3$. Calculated (%): C, 71.56; H, 6.71; N, 4.91. IR, ν/cm^{-1}: 1660, 1705, 1720. ^{1}H NMR ($CDCl_3$), δ: 1.40—1.55, 1.80—1.95 (both m, 2 H each, CH_2); 2.15 (s, 3 H, COMe, *cis*); 2.25 (s, 3 H, COMe, *trans*); 2.30, 2.84 (both m, 1 H each, CH); 3.50 (m, 2 H, CH_2); 4.65 (m, 1 H, CH); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 18.01, 18.17, 25.30, 27.64, 28.04, 28.27, 30.44, 30.58; 32.02, 50.08, 65.62, 126.79, 128.08, 130.03, 135.66, 169.44, 205.55, 205.76.

Methyl 2-(1-benzoylpyrrolidine-2-carbonyl)cyclopropanecarboxylate (9) was obtained as a light yellow oil. The yield of compound **9** was 0.24 g (80%). Found (%): C, 67.55; H, 6.25; N, 4.05. $C_{17}H_{19}NO_4$. Calculated (%): C, 67.76; H, 6.36; N, 4.65. IR, ν/cm^{-1}: 1650, 1730, 1750. ^{1}H NMR ($CDCl_3$), δ: 1.28—1.51 (m, 2 H, CH_2); 1.85 (m, 1 H, CH); 1.95—2.05, 2.15—2.41 (both m, 2 H each, CH_2); 2.50—2.60 (m, 1 H, CH); 3.45—3.55 (m, 2 H, CH_2); 3.60 (s, 3 H, CO_2Me, *cis*); 3.80 (s, 3 H, CO_2Me, *trans*); 4.85 (m, 1 H, CH); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 17.09, 17.37, 23.76, 24.09, 25.35, 26.37; 26.49; 28.27, 50.15, 52.12, 65.65, 127.19, 128.20, 130.13, 135.93, 169.58, 172.54, 204.94.

2-(1-Benzoylpyrrolidine-2-carbonyl)cyclopropane-1-carbonitrile (10a). ^{1}H NMR ($CDCl_3$), δ: 3.75 (m, 2 H, CH_2N); 4.95 (m, 1 H, CHN); 7.30—7.60 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 6.98, 16.42, 24.46, 25.08, 28.25, 50.26, 65.92, 119.68, 127.28, 127.42, 128.38, 130.55, 135.48, 135.58, 169.86, 203.63.

1-(1-Benzoylpyrrolidine-2-carbonyl)cyclopropane-1-carbonitrile (10b). ^{1}H NMR ($CDCl_3$), δ: 3.55 (m, 2 H, CH_2N); 5.05 (m, 1 H, CHN); 7.30—7.60 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 17.42, 21.61, 21.72, 25.56, 28.45, 50.03, 64.89, 120.27, 127.28, 127.42, 128.38, 130.55, 135.48, 135.58, 169.63, 199.42.

The mixture of nitriles **10a** and **10b** was obtained as a light yellow oil. The total yield was 0.21 g (82%). Found (%): C, 71.54; H, 5.95; N, 10.15. $C_{16}H_{16}N_2O_2$. Calculated (%): C, 71.62; H, 6.01; N, 10.44. **10a** + **10b**: IR, ν/cm^{-1}: 1650, 1730, 2260.

1-Benzoyl-2-(2-dimethylsulfuranylidene-1,3-dioxobutyl)pyrrolidine (11). Ylide **1** (0.28 g, 1 mmol) was dissolved under heating in 8 mL of dry toluene to give a yellow solution. Acetic anhydride (0.11 g, 1 mmol) was added dropwise, and the resulting colorless solution was refluxed for 1 h. The solvent was removed to give ylide **11** as a light yellow oil. The yield of compound **11** was 0.27 g (95%). Found (%): C, 63.21; H, 6.42; N, 4.23; S, 9.78. $C_{17}H_{21}NO_3S$. Calculated (%): C, 63.92; H, 6.63; N, 4.39; S, 10.04. IR, ν/cm^{-1}: 1580, 1650. ^{1}H NMR ($CDCl_3$), δ: 1.85—2.10 (m, 4 H, 2 CH_2); 2.35 (s, 3 H, Me); 3.05, 3.10 (both s, 3 H each, SMe_2); 3.50—3.80 (m, 2 H, CH_2); 5.45 (t, 1 H, CH, J = 7.05 Hz); 7.30—7.60 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 25.42, 26.11, 26.82, 27.21, 31.95, 63.50, 86.23, 127.0, 128.02, 129.74, 136.51, 169.12, 170.29, 176.12.

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