Sulfonium ylides

6.* New reaction of intramolecular cyclization of phthalimido-containing keto-stabilized sulfonium ylides

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The thermal transformations of phthalimido-substituted keto-stabilized sulfonium ylides, including optically active ylides, were studied. The thermolysis of sulfonium ylides obtained from α- and β-amino acids leads to methylthio-substituted pyrrolizidine- and indolizidinediones. Racemization of optically active ylides does not occur. Sulfonium ylides with longer carbon chains do not undergo intramolecular cyclization.

Key words: sulfonium ylides, thermolysis, intramolecular cyclization; pyrrolizidinedione; indolizidinedione.

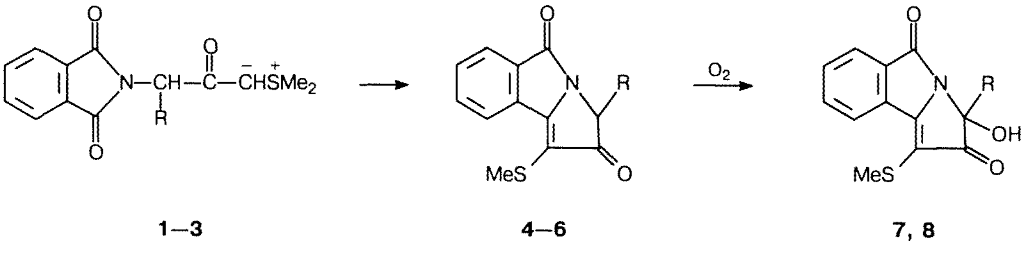
Sulfonium ylides containing an oxo group separated from the carbanionic center by several atoms undergo cyclization by a mechanism typical of such compounds, involving the formation of an oxirane ring and elimination of a disulfide molecule.[1—3] The synthesis of sulfonium ylides from amino acids containing a phthalimide fragment[4] allowed us to study the interaction of the ylide C atom with the carbonyl of the imide group. It was found that reactions involving sulfonium ylides obtained from α-amino acids occur by intramolecular cyclization accompanied by elimination of a methanol molecule.[5] For example, heating ylides **1—3** in acetonitrile at 80 °C for 3 h resulted in the corresponding methylthio-substituted pyrrolizidinediones **4—6** in yields not exceeding 25 % (Scheme 1). Thermolysis of these ylides without a solvent under reduced pressure (15 Torr) allowed us to increase the yields of the products to 35 %. Thermolysis of optically active sulfonium ylides **1** and **3** does not cause racemization of the asymmetric carbon atoms.

Heating the reaction mixture in acetonitrile for 5—8 h results in pyrrolizidinediones **5** and **6**. Under these conditions, they are oxidized with oxygen in air to give tertiary alcohols **7** and **8**, respectively, which were isolated in yields no higher than 7 % (see Scheme 1).

Cyclization of sulfonium ylide **9** obtained from β-alanine, whose carbanionic center is separated by four atoms from the carbonyl groups in the phthalimide fragment, gave indolizidinedione (**10**) in 27 % yield (Scheme 2).[6]

It is known that intramolecular Wittig reaction involving similar phosphonium ylides can be facilitated by adding an equimolar amount of benzoic acid in toluene.[7] Cyclization of sulfonium ylides **1—3** and **9** in the presence of an equimolar amount of benzoic acid (toluene, 110 °C) allowed us to increase the yield of products **4—6** and **10** to 86 %. The reaction mixture was found to contain methyl benzoate.

Scheme 1



R = Me (**1**, **4**), Pr^i (**2**, **5**, **7**), Bn (**3**, **6**, **8**)

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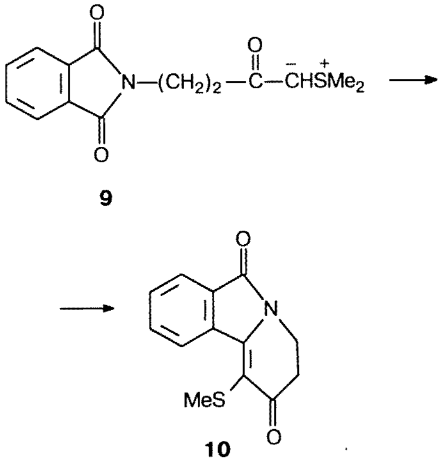
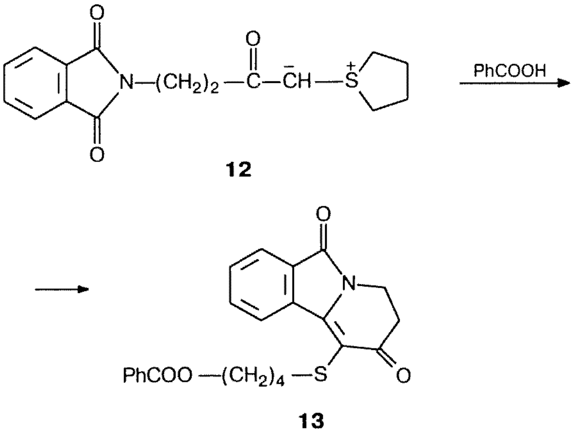
* For Part 5, see *Izv. Akad. Nauk, Ser. Khim.*, 1992, 720 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 566 (Engl. Transl.)].

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 165—168, January, 1996.

Scheme 2



Scheme 3



In the case of sulfonium ylide **12** obtained from sulfonium salt **11** and containing a thiophane fragment, the resulting indolizidinedione **13** incorporates a benzoate moiety (Scheme 3).

The reactions of sulfonium ylides **14** and **15** synthesized from γ- and δ-amino acids, respectively, and containing longer carbon chains do not result in formation of seven- or eight-membered rings. In both cases, oxosulfides (**16** and **17**, respectively) and oxobenzoates (**18** and **19**, respectively) were identified as the main products and their structures were established by spectral data (Scheme 4).

The structures of the pyrrolizidinediones were unambiguously proved by X-ray diffraction analysis.[8] The ^{13}C NMR spectra have been considered in our previous paper.[9]

Experimental

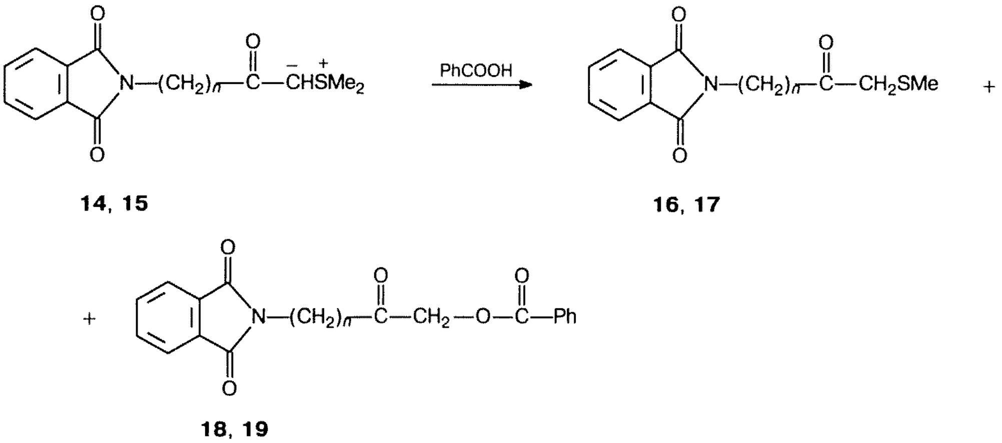
IR spectra were recorded on a Specord M-80 spectrophotometer (in thin layers or in Vaseline oil). ^{1}H NMR spectra were recorded on Tesla BS-480B and Bruker AM-300 spectrometers (100 and 300 MHz, respectively). ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument (75 MHz) using $SiMe_4$ as the internal standard. Optical rotations were determined on a Perkin Elmer-141 polarimeter.

Procedures for synthesizing the starting sulfonium ylides **1—3**, **9**, **14**, and **15** and the spectral characteristics of these compounds have already been reported.[4]

Thermolysis of ylides in toluene in the presence of benzoic acid (general procedure). An ylide (0.002 mol) was dissolved with heating in dry toluene (8 mL). Benzoic acid (0.002 mol) was added, and the mixture was heated for 30 min with a reflux condenser. The toluene was distilled off, and the reaction product was chromatographed on a column with SiO_2 using ethyl acetate—hexane as the eluent.

3-Methyl-1-methylthio-3*H*-pyrrole[2,1-*a*]isoindole-2,5-dione (4). Yield 85 %, m.p. 145—147 °C, $[\alpha]_D^{23}$ −3.1° (*c* 1.67, $CHCl_3$). IR, ν/cm^{-1}: 1604, 1714, 1740, 1776. ^{1}H NMR ($CDCl_3$), δ: 1.67 (d, 3 H, CH_3, *J* = 7 Hz); 2.54 (s, 3 H, SCH_3); 4.40 (q, 1 H, CH, *J* = 7 Hz); 7.75 and 8.24 (both m, 4 H, C_6H_4). Found (%): C, 63.62; H, 4.48; N, 5.69;

Scheme 4



n = 3 (**14**, **16**, **18**), 4 (**15**, **17**, **19**)

S, 12.98. $C_{13}H_{11}NO_2S$. Calculated (%): C, 63.65; H, 4.52; N, 5.71; S, 13.07.

3-Isopropyl-1-methylthio-3*H*-pyrrole[2,1-*a*]isoindole-2,5-dione (5). Yield 84 %, m.p. 135—137 °C. IR, ν/cm^{-1}: 1620, 1713, 1777, 1737. ^{1}H NMR ($CDCl_3$), δ: 1.05 and 1.10 (both d, 6 H, CH_3, *J* = 6.8 Hz); 2.52 (s, 3 H, SCH_3); 2.72 (sept, 1 H, CH, *J* = 7.04 Hz); 4.32 (d, 1 H, CH, *J* = 3.05 Hz); 7.75 (m, 3 H, C_6H_4); 8.26 (m, 1 H, C_6H_4). Found (%): C, 65.74; H, 5.28; N, 5.10; S, 11.54. $C_{15}H_{15}NO_2S$. Calculated (%): C, 65.91; H, 5.53; N, 5.12; S, 11.73.

3-Benzyl-1-methylthio-3*H*-pyrrole[2,1-*a*]isoindole-2,5-dione (6). Yield 83 %, m.p. 128—131 °C, $[\alpha]_D^{23}$ −16.44° (*c* 2.60, $CHCl_3$). IR, ν/cm^{-1}: 1600, 1716, 1776, 1745. ^{1}H NMR ($CDCl_3$), δ: 2.27 (s, 3 H, SCH_3); 3.58 (s, 2 H, CH_2); 4.67—5.46 (m, 1 H, CH); 7.07 (br.s, 5 H, C_6H_5); 7.74 (m, 4 H, C_6H_4). Found (%): C, 70.98; H, 4.73; N, 4.25; S, 9.70. $C_{19}H_{15}NO_2S$. Calculated (%): C, 71.0; H, 4.70; N, 4.36; S, 9.98.

3-Hydroxy-3-isopropyl-1-methylthio-3*H*-pyrrole[2,1-*a*]isoindole-2,5-dione (7). Compound **2** (1 g, 0.003 mol) was heated in toluene (20 mL) for 8 h. Separation of thermolysis products by column chromatography on SiO_2 using ethyl acetate—hexane (1 : 1) as the eluent gave 0.05 g (5 %) of a yellow crystalline compound, m.p. 135—137 °C. IR, ν/cm^{-1}: 1584, 1608, 1712, 3408. ^{1}H NMR ($CDCl_3$), δ: 1.04 and 1.07 (both d, 6 H, 2 CH_3, *J* = 6.81 Hz); 2.53 (s, 3 H, SCH_3); 2.77 (sept, 1 H, CH, *J* = 6.81 Hz); 7.73—8.36 (m, 4 H, C_6H_4). Found (%): C, 60.58; H, 5.26; N, 4.70; S, 10.78. $C_{15}H_{15}NO_3S \cdot 0.5\ H_2O$. Calculated (%): C, 60.38; H, 5.41; N, 4.69; S, 10.75.

3-Benzyl-3-hydroxy-1-methylthio-3*H*-pyrrole[2,1-*a*]isoindole-2,5-dione (8) was obtained from ylide **3** similarly to compound **7**, yield 7 %, m.p. 189—191 °C. IR, ν/cm^{-1}: 1608, 1720, 1776, 3448. ^{1}H NMR ($CDCl_3$), δ: 2.26 (s, 3 H, SCH_3); 3.51 and 3.84 (both d, each 1 H, CH_2, *J* = 13.1 Hz); 7.77—8.36 (m, 4 H, C_6H_4). Found (%): C, 66.18; H, 4.38; N, 4.01; S, 9.20. $C_{19}H_{15}NO_3S \cdot 0.5\ H_2O$. Calculated (%): C, 66.10; H, 4.66; N, 4.04; S, 9.26.

1-Methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,5-dione (10). Compound **9** (0.5 g, 0.0018 mol) was dissolved with heating in dry toluene (8 mL), benzoic acid (0.2 g, 0.0018 mol) was added, and the reaction mixture was heated for 1 h with a reflux condenser. The toluene was distilled off, and the product was isolated by chromatography on a column with SiO_2 using ethyl acetate—hexane (1 : 1) as the eluent to give 0.28 g (86 %) of compound **10**, m.p. 164—165 °C. IR, ν/cm^{-1}: 1664, 1712, 1770. ^{1}H NMR ($CDCl_3$), δ: 2.39 (s, 3 H, CH_3S); 2.86 (t, 2 H, CH_2CO, *J* = 7 Hz); 4.14 (t, 2 H, CH_2, *J* = 7 Hz); 7.68 and 8.90 (both m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 17.76 (q, C(11)); 35.97 (t, C(3)); 36.82 (t, C(4)); 113.38 (s, C(1)); 123.89 (d, C(7)); 127.55 (d, C(10)); 129.83 (s, C(6a)); 131.92 (C(8)); 133.04 (d, C(9)); 134.47 (s, C(10a)); 151.11 (s, C(10b)); 165.35 (s, C(6)); 190.87 (s, C(2)). Found (%): C, 63.70; H, 4.45; N, 5.68; S, 12.87. $C_{13}H_{11}NO_2S$. Calculated (%): C, 63.65; H, 4.52; N, 5.71; S, 13.07.

4-Phthalimido-2-oxobutyltetramethylenesulfonium bromide (11) was obtained by a procedure reported previously,[4] yield 85 %, m.p. 125 °C. IR, ν/cm^{-1}: 1708, 1776. ^{1}H NMR (CF_3COOH), δ: 2.0 (m, 4 H, CH_2CH_2); 2.82 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.25 (m, 4 H, CH_2SCH_2); 3.72 (t, 2 H, NCH_2, *J* = 7 Hz); 4.35 (s, 2 H, CH_2S); 7.45 (br.s, 4 H, C_6H_4). Found (%): C, 49.85; H, 4.60; Br, 20.17; N, 3.65; S, 8.20. $C_{16}H_{18}BrNO_3S$. Calculated (%): C, 50.0; H, 4.72; Br, 20.79; N, 3.64; S, 8.34.

4-Phthalimido-1-tetramethylenesulfuranylidenebutane-2-one (12) was obtained by a procedure reported previously,[4] yield 91 %. IR, ν/cm^{-1}: 1535, 1690, 1769. ^{1}H NMR ($CDCl_3$), δ: 1.99 and 2.50 (both m, each 2 H, CH_2CH_2); 2.45 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.05 and 3.45 (both m, 4 H, CH_2SCH_2); 3.59 (s, 1 H, CH); 3.69 (t, 2 H, CH_2, *J* = 7 Hz); 7.71 (m, 4 H, C_6H_4). Found (%): C, 63.11; H, 5.24; N, 4.38; S, 10.49. $C_{16}H_{17}NO_3S$. Calculated (%): C, 63.34; H, 5.65; N, 4.62; S, 10.57.

1-Benzoyloxybutylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (13). Yield 54 %. IR, ν/cm^{-1}: 1572, 1668, 1712. ^{1}H NMR ($CDCl_3$), δ: 1.75 and 1.96 (both m, each 2 H, CH_2CH_2); 2.82 (t, 2 H, CH_2CO, *J* = 7.3 Hz); 2.95 (t, 2 H, SCH_2, *J* = 7.3 Hz); 4.12 (t, 2 H, NCH_2, *J* = 7.3 Hz); 4.35 (t, 2 H, CH_2O, *J* = 7.5 Hz); 7.35—9.02 (m, 9 H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 26.50 (t, C(12)); 27.87 (t, C(13)); 33.21 (t, C(11)); 35.84 (t, C(3)); 36.82 (t, C(4)); 64.17 (t, C(14)); 111.62 (s, C(1)); 123.82 (d, C(7)); 127.55 (d, C(10)); 130.09 (s, C(6a)); 131.92 (d, C(8)); 132.90 (d, C(9)); 134.53 (s, C(10a)); 132.90 (d) and 166.33 (s) (PhCOO). Found (%): C, 67.80; H, 5.17; N, 3.48; S, 7.18. $C_{23}H_{21}NO_4S$. Calculated (%): C, 67.79; H, 5.19; N, 3.44; S, 7.87.

1-Methylthio-5-phthalimido-2-oxopentane (16) was obtained from compound **14** by the general thermolysis procedure in the presence of benzoic acid and was isolated by column chromatography in 39 % yield. IR, ν/cm^{-1}: 1620, 1710, 1720, 1770. ^{1}H NMR ($CDCl_3$), δ: 2.05 (s, 3 H, SCH_3); 1.92—2.17 (m, 2 H, CH_2); 2.59 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.19 (s, 2 H, SCH_2); 3.73 (t, 2 H, NCH_2, *J* = 7 Hz); 7.76 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 15.66 (q, CH_3S); 22.19, 35.90, 37.14, 42.92 (t, 4 CH_2); 204.25 (s, CO); 123.18 (d), 131.99 (s), 133.94 (d) and 168.35 (s) (phthalyl). Found (%): C, 60.53; H, 5.18; N, 5.03; S, 10.46. $C_{14}H_{15}NO_3S$. Calculated (%): C, 60.63; H, 5.45; N, 5.05; S, 11.56.

1-Benzoyloxy-2-oxo-5-phthalimidopentane (18). Yield 37 %. IR, ν/cm^{-1}: 1712, 1768. ^{1}H NMR ($CDCl_3$), δ: 1.93—2.10 (m, 2 H, CH_2); 2.68 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.74 (t, 2 H, NCH_2, *J* = 7 Hz); 4.90 (s, 2 H, CH_2O); 7.75 (m, 5 H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 22.85, 35.91, 37.01, 69.35 (t, 4 CH_2); 202.88 (s, CO); 123.18 (d), 131.99 (s), 133.94 (d) and 168.35 (s) (phthalyl); 128.39, 129.83, 133.95, 165.73 (PhCO). Found (%): C, 68.35; H, 4.89; N, 3.90. $C_{20}H_{17}NO_5$. Calculated (%): C, 68.37; H, 4.88; N, 3.96.

Compounds **17** and **19** were obtained from **15** under conditions similar to those reported for **16** and **18**.

1-Methylthio-2-oxo-6-phthalimidohexane (17). Yield 40 %. IR, ν/cm^{-1}: 1620, 1710, 1720, 1770. ^{1}H NMR ($CDCl_3$), δ: 1.65 (m, 4 H, CH_2CH_2); 2.06 (s, 3 H, CH_3); 2.68 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.16 (s, 2 H, SCH_2); 3.70 (t, 2 H, NCH_2, *J* = 7 Hz); 7.75 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 15.66 (q, SCH_3); 21.02, 27.94, 37.53, 39.29, 42.89 (t, 5 CH_2); 123.18 (d), 133.56 (s), 133.88 (s), and 168.34 (s) (phthalyl); 204.84 (s, CO). Found (%): C, 61.80; H, 5.73; N, 4.80; S, 10.18. $C_{15}H_{17}NO_3S$. Calculated (%): C, 61.82; H, 5.88; N, 4.81; S, 11.00.

1-Benzoyloxy-2-oxo-6-phthalimidohexane (19). Yield 39 %. IR, ν/cm^{-1}: 1712, 1768. ^{1}H NMR ($CDCl_3$), δ: 1.72 (m, 4 H, CH_2CH_2); 2.58 (t, 2 H, CH_2CO, *J* = 7 Hz); 3.71 (t, 2 H, NCH_2, *J* = 7 Hz); 4.87 (m, 2 H, CH_2O); 7.38—8.13 (m, 9 H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 20.33, 27.95, 37.41, 38.09, 68.44 (t, 5 CH_2); 123.25 (d), 133.40 (s), 133.92 (d), and 168.38 (s) (phthalyl); 128.50, 129.92, 132.19, 165.96 (PhCO); 203.47 (s, CO). Found (%): C, 68.75; H, 5.12; N, 3.80. $C_{21}H_{19}NO_5S$. Calculated (%): C, 69.03; H, 5.24; N, 3.83.

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