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Sulfur ylides
15.* Intramolecular cyclization of new keto-stabilized sulfur bis-ylide

F. Z. Galin,★ I. M. Sakhautdinov, I. G. Khalikov, S. N. Lakeev, I. O. Maidanova, and A. A. Fatykhov

Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences,
71 prosp. Oktyabrya, 450054 Ufa, Russian Federation.
Fax: +7 (347) 235 6066, 235 2641. E-mail: galin@anrb.ru, irina_m@anrb.ru

New sulfur bis-ylide was obtained from 3-amino-3-phenylpropionic acid and pyromellitic dianhydride. Its intramolecular cyclization proceeds regioselectively, leading to 3,4,11,12-tetrahydro-2*H*,6*H*-indolizino[2,1-*f*]pyrido[2,1-*a*]isoindole derivative in 66% yield. Phosphorus bis-ylide of similar structure gives a cyclization product in 10% yield.

Key words: 3-amino-3-phenylpropionic acid, pyromellitic dianhydride, sulfur ylides, phosphorus ylides, heterocyclization, 2*H*,6*H*-indolizino[2,1-*f*]pyrido[2,1-*a*]isoindoles, pyrrolo[3,4-*f*]isoindole-1,3,5,7-tetraones.

In continuation of the research on intramolecular cyclization of keto-stabilized sulfonium ylides, *viz.*, derivatives of *N*-protected α- and β-amino acids,[1—9] in the present study the synthesis of sulfur bis-ylide **1a** was accomplished (Scheme 1), starting from the condensation product of 3-amino-3-phenylpropionic acid (β-phenyl-β-alanine) **2** and pyromellitic dianhydride (**3**).

Pyromellitic dianhydride (**3**) and 3-amino-3-phenylpropionic acid (**2**), taken in the ratio 1 : 2, upon heating in nitrobenzene (155—160 °C) gave diacid **4**, which was then converted into the polymeric anhydride upon treatment with methyl chloroformate in the presence of equimolar amount of *N*-methylmorpholine. The anhydride, without isolation from the reaction mixture, was treated with a solution of CH_2N_2 in CH_2Cl_2 to afford didiazo diketone **5** in 76% yield. The reaction of didiazo diketone **5** with aqueous HBr afforded dibromo diketone **6**, which reacted with Me_2S to form disulfonium salt **7a**. The deprotonation of salt **7a** with sodium hydride led to sulfur bis-ylide **1a**.

The heating of ylide **1a** in boiling toluene in the presence of equimolar amount of benzoic acid gives the product of intramolecular cyclization **8a** in 66% yield. The reaction proceeds regiospecifically to form the isomer with the cisoid mutual junction of the dihydropyridinone rings at the pyrroloisoindole tricycle.

The structure of product **8a** was confirmed by spectral characteristics. The presence of two signals of H(7) and H(14) protons of the aromatic ring at δ_H 8.31 and 9.45 of the ^{1}H NMR spectrum (rather than of one signal of the two protons, which would have been characteristic of the transoid junction) serves as the evidence of the cisoid junction. In the ^{13}C NMR spectrum, signals of the corresponding carbon atoms resonate at δ_C 122.71 and 125.87.

Signals of two thiomethyl group are also informative: in the ^{1}H NMR spectrum, there is a singlet of six protons at δ_H 2.45, as well as a signal of two carbon atoms at δ_C 17.76 of the ^{13}C NMR spectrum. Mutual orientation of the phenyl groups at C(4) and C(10) atoms of the pentacyclic framework was not established by NMR. Nevertheless, formation of the individual isomer, when racemic β-phenyl-β-alanine was used in the synthesis, is noteworthy.

It is known that phosphorus ylides readily react with carbonyl group to form a double bond (the Wittig reaction). A comparison of the reactivity of sulfur ylide **1a** and phosphorus ylide **1b** under the intramolecular cyclization conditions showed that the latter gives a complicated mixture of products, from which the polycyclic product **8b** was isolated in 10% yield. Phosphorus ylide **1b** was synthesized from dibromo diketone **6** upon treatment with PPh_3 and by subsequent deprotonation of phosphonium salt **7b** with a mixture of NaOH and K_2CO_3.

In conclusion, on the basis of the condensation product of β-phenyl-β-alanine (**2**) and pyromellitic dianhydride (**3**), the new keto-stabilized sulfur bis-ylide **1a** was synthesized, which upon heating in the presence of equimolar amount of benzoic acid gives the product of intramolecular cyclization **8a** in 66% yield. The reaction proceeds regio- and stereospecifically to form the substituted 3,4,10,11-tetrahydro-2*H*,6*H*-indolizino[2,1-*f*]-pyrido[2,1-*a*]isoindole **8a**.

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* For Part 14, see Ref. 1

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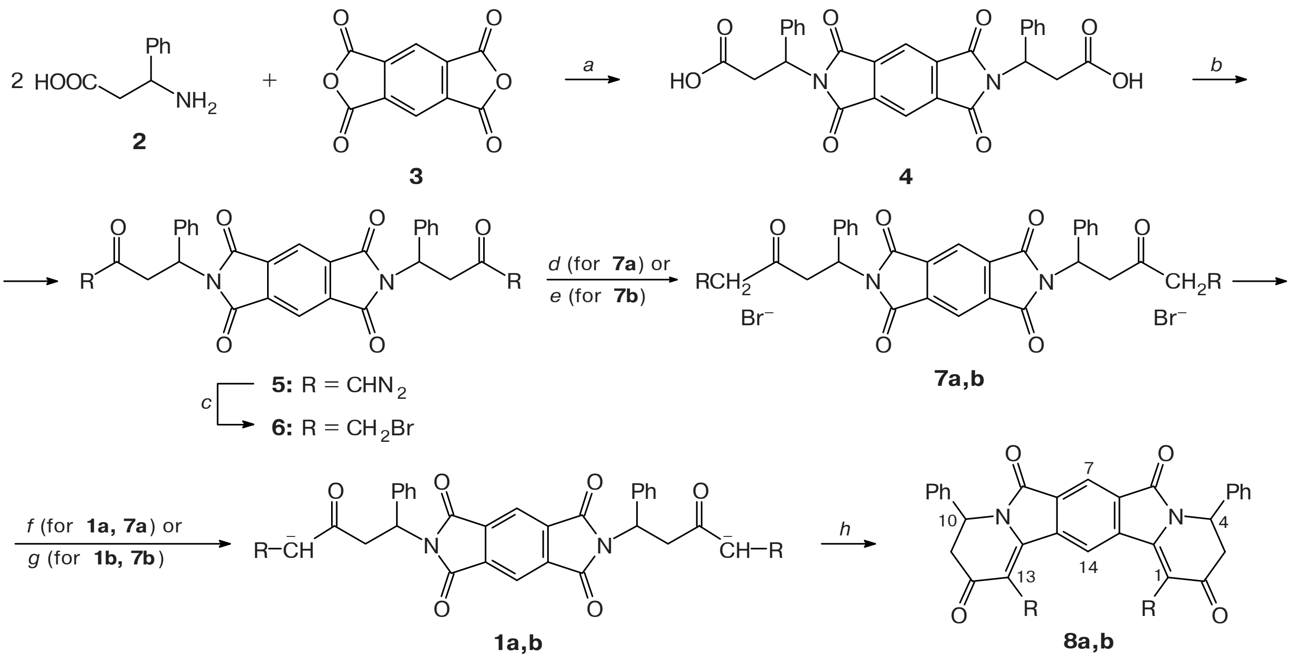
Scheme 1



R = $^{+}SMe_2$ (**1a, 7a**), SMe (**8a**); $^{+}PPh_3$ (**1b, 7b**), H (**8b**)

Reagents and conditions: *a*. $PhNO_2$, 155—160 °C; *b*. ClCOOMe, then, CH_2N_2, THF, 0 °C; *c*. HBr, CH_2Cl_2, 20 °C; *d*. Me_2S, Me_2CO; *e*. PPh_3, Me_2CO; *f*. NaH, THF; *g*. NaOH, K_2CO_3, $CHCl_3$; *h*. $PhCO_2H$, $PhCH_3$.

Experimental

IR spectra were recorded on a UR-20 and Specord M-80 spectrometers (in Nujol), ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 and 75 MHz, respectively) for solutions in $CDCl_3$ (except for the spectrum of **8b**), Me_4Si was used as the internal standard. The reaction course was monitored by TLC on Silufol UV-254 plates with visualization of substances in the UV light, iodine vapors, and by spraying of the plates with ninhydrin solution or with anisaldehyde solution with subsequent heating at 100—120 °C. Acetone, CCl_4, and nitrobenzene were distilled over P_2O_5, *N*-methylmorpholine, over KOH. Toluene, THF, and light petroleum were refluxed and distilled over sodium metal, CH_2Cl_2 was distilled, Me_2S was dried over molecular sieves 4 Å. Hydrobromic acid was used as the 48% aq. solution (pure for analysis grade), NaH, as the 60—65% dispersion in oil (Fluka). Pyromellitic dianhydride **3** (pure grade), racemic 3-amino-3-phenylpropionic acid (β-phenyl-β-alanine, pure grade), PPh_3 (pure grade), methyl chloroformate (pure for analysis grade), and benzoic acid (pure grade) were used without additional purification.

2,6-Bis(3-hydroxy-3-oxo-1-phenylprop-1-yl)pyrrolo[3,4-*f*]-isoindole-1,3,5,7(2*H*,6*H*)-tetraone (4). A solution of pyromellitic dianhydride **3** (2 g, 10 mmol) and (±)-β-phenyl-β-alanine **2** (3.3 g, 20 mmol) in nitrobenzene (100 mL) was vigorously stirred for 1 h at 155—165 °C. Then, the reaction mixture was cooled to ~20 °C, diacid **4** formed was filtered off, washed with light petroleum, and dried in air. The yield was 5.1 g (95%), m.p. 276—278 °C. Found (%): C, 65.62; H, 3.9; N, 5.45; $C_{28}H_{20}N_2O_8$. Calculated (%): C, 65.62; H, 3.93; N, 5.47. IR, ν/cm^{-1}: 1686, 1750, 3548.

2,6-Bis(4-diazo-3-oxo-1-phenylbut-1-yl)pyrrolo[3,4-*f*]-isoindole-1,3,5,7(2*H*,6*H*)-tetraone (5). Methyl chloroformate (1 mL, 12.9 mmol) was added to a suspension of diacid **4** (5.1 g, 10 mmol) in anhydrous THF and then, *N*-methylmorpholine (1.8 mL, 12.9 mmol) was added dropwise at 0 °C. This was stirred for 30 min and the precipitate of *N*-methylmorpholine hydrochloride formed was quickly filtered off. Then, a solution of CH_2N_2 (obtained from 87 mmol of *N*-nitrozomethylurea) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C to a solution of the polymeric anhydride obtained. The product was isolated by column chromatography (eluent, light petroleum—ethyl acetate, 2 : 1). The yield was 4.26 g (76%), m.p. 94—97 °C. Found (%): C, 64.26; H, 3.9; N, 14.96. $C_{30}H_{20}N_6O_6$. Calculated (%): C, 64.28; H, 3.6; N, 14.99. IR, ν/cm^{-1}: 1698, 1740, 2120. ^{1}H NMR, δ: 3.05—3.55 (m, 4 H, CH_2); 4.32 (s, 2 H, CHN_2); 5.85—5.98 (m, 2 H, CH—N); 7.22—7.58 (m, 10 H, Ph); 8.19 (s, 2 H, C_6H_2). ^{13}C NMR, δ: 47.95, 50.98, 51.72, 118.56, 127.70, 128.57, 129.13, 137.04, 138.28, 166.17, 199.69.

2,6-Bis(4-bromo-3-oxo-1-phenylbut-1-yl)pyrrolo[3,4-*f*]-isoindole-1,3,5,7(2*H*,6*H*)-tetraone (6). Hydrobromic acid (2 mL of 48% aq. solution) was added to a stirred solution of didiazo diketone **5** (0.56 g, 1 mmol) in CH_2Cl_2 (20 mL) at ~20 °C. After the evolution of gas was over, the solution was stirred for another 1 h. Organic layer was separated, washed with 5% Na_2CO_3 (aq.), and dried with $MgSO_4$. The solvent was evaporated and the product was isolated by column chromatography (eluent, light petroleum—ethyl acetate, 4 : 1). The yield was 0.6 g (90%), m.p. 108—110 °C. Found (%): C, 54.04; H, 3.39; Br, 23.97; N, 4.4. $C_{30}H_{22}Br_2N_2O_6$. Calculated (%): C, 54.08; H, 3.33; Br, 23.98; N, 4.2. IR, ν/cm^{-1}: 1696, 1745. ^{1}H NMR, δ: 3.51, 3.92 (both s, 4 H each, CH_2); 5.83—5.88 (m, 2 H, CH); 7.22—7.74 (m, 10 H, Ph); 8.18 (s, 2 H, C_6H_2). ^{13}C NMR, δ: 33.78, 40.98, 50.94, 118.44, 127.59, 128.52, 128.93, 129.22, 136.78, 165.94, 198.81.

2,6-Bis(4-dimethylsulfonio-3-oxo-1-phenylbut-1-yl)pyrrolo[3,4-*f*]isoindole-1,3,5,7(2*H*,6*H*)-tetraone dibromide (7a). Dimethyl sulfide (0.192 g, 6 mmol) was added to a stirred solution of dibromo diketone **6** (0.67 g, 1 mmol) in anhydrous acetone (10 mL) and the mixture was kept for ~14 h. The precipitate formed was filtered off and washed with acetone. The yield was 0.54 g (68%), m.p. 214—218 °C. Found (%): C, 52.08; H, 4.25; Br, 20.16; N, 3.43; S, 8.11. $C_{34}H_{34}Br_2N_2O_6S_2$. Calculated (%): C, 51.65; H, 4.33; Br, 20.21; N, 3.54; S, 8.11. IR, ν/cm^{-1}: 1686, 1750, 1764.

2,6-Bis[4-(dimethyl-λ^4-sulfanylidene)-3-oxo-1-phenylbut-1-yl]pyrrolo[3,4-*f*]isoindole-1,3,5,7(2*H*,6*H*)-tetraone (1a). Sodium hydride (0.053 g, 2.2 mmol) was added in one portion to a stirred suspension of bis-sulfonium salt **7a** (2.37 g, 3 mmol) in anhydrous THF (10 mL) at ~20 °C under argon atmosphere. The reaction mixture was stirred for 30 min, then, filtered, and dried with K_2CO_3. The solvent was evaporated, ylide **1a** was used in the subsequent reaction without additional purification. The yield was 1.2 g (63%). Found (%): C, 64.56; H, 5.15; N, 4.46; S, 10.32. $C_{34}H_{32}N_2O_6S_2$. Calculated (%): C, 64.95; H, 5.13; N, 4.46; S, 10.2. IR, ν/cm^{-1}: 1560, 1686, 1750.

1,13-Bis(methylthio)-4,10-diphenyl-3,4,10,11-tetrahydro-2*H*,6*H*-indolizino[2,1-*f*]pyrido[2,1-*a*]isoindole-2,6,8,12-tetraone (8a). Sulfur bis-ylide **1a** (0.63 g, 1 mmol) was dissolved in anhydrous toluene (20 mL) under heating, $PhCO_2H$ (0.12 g, 1 mmol) was added, and this was refluxed for 30 min. Toluene was evaporated, the residue was subjected to chromatography (eluent, acetone—chloroform, 1 : 9). The yield was 0.37 g (66%), m.p. 84—88 °C. Found (%): C, 68.42; H, 4.29; N, 4.92; S, 11.3. $C_{32}H_{24}N_2O_4S_2$. Calculated (%): C, 68.06; H, 4.28; N, 4.96; S, 11.36. IR, ν/cm^{-1}: 1686, 1750, 3548. ^{1}H NMR, δ: 2.98 (s, 6 H, Me); 3.25 (d, 2 H, CH_2, $J = -15.3$ Hz); 3.69 (dd, 2 H, CH_2, $J = -15.3$ Hz, $J = 6.9$ Hz); 5.96 (d, 2 H, CH, $J = 6.9$ Hz); 7.22—7.62 (m, 10 H, Ph); 8.29, 9.45 (both s, 1 H each, C_6H_2). ^{13}C NMR, δ: 17.77, 42.46, 51.57, 65.74, 122.71, 125.87, 128.5, 128.86, 129.19, 137.88, 148.98, 163.07, 189.49.

2,6-Bis(3-oxo-4-triphenylphosphonio-1-phenylbut-1-yl)pyrrolo[3,4-*f*]isoindole-1,3,5,7(2*H*,6*H*)-tetraone dibromide (7b). A solution of PPh_3 (0.37 g, 1.4 mmol) in acetone (5 mL) was added to a stirred solution of dibromo diketone **6** (0.47 g, 0.7 mmol) in anhydrous acetone (5 mL) and the mixture was kept for 12 h. The precipitate formed was filtered off and washed with acetone. The yield was 0.52 g (63%), m.p. 281—283 °C. Found (%): C, 66.02; H, 4.08; Br, 13.69; N, 2.35; P, 5.24. $C_{66}H_{52}Br_2N_2O_6P_2$. Calculated (%): C, 66.11; H, 4.16; Br, 13.74; N, 2.41; P, 5.33. IR, ν/cm^{-1}: 742, 1440, 1462, 1712, 1743.

2,6-Bis[3-oxo-1-phenyl-4-(triphenyl-λ^5-phosphoranylidene)but-1-yl]pyrrolo[3,4-*f*]isoindole-1,3,5,7(2*H*,6*H*)-tetraone (1b). A mixture of 12.5 *M* NaOH (1.4 mL) and saturated aq. K_2CO_3 (8 mL) was added in one portion to a stirred suspension of diphosphonium salt **7b** (6.7 g, 5.6 mmol) in $CHCl_3$ (10 mL) at 10 °C and the mixture was stirred at this temperature for 30 min. The temperature was raised to ~20 °C, the mixture was filtered, the organic layer was separated and dried with K_2CO_3. The solvent was evaporated, ylide **1b** was used in the subsequent reaction without additional purification. The yield was 5.5 g (96%), m.p. 210—212 °C. Found (%): C, 77.13; H, 5.09; N, 2.58; P, 5.77. $C_{66}H_{50}N_2O_6P_2$. Calculated (%): C, 77.03; H, 4.90; N, 2.72; P, 6.02. IR, ν/cm^{-1}: 1550, 1708, 1732.

4,10-Diphenyl-3,4,8,10,11-tetrahydro-2*H*,6*H*-indolizino[2,1-*f*]pyrido[2,1-*a*]isoindole-2,6,8,12-tetraone (8b). Benzoic acid (5 mg, 0.04 mmol) was added to a solution of phosphorus bis-ylide **1b** (0.2 g, 0.2 mmol) in anhydrous toluene (20 mL) and the mixture was refluxed for 6 h. The solvent was evaporated, the product was isolated by column chromatography (eluent, light petroleum—ethyl acetate, 2 : 1). The yield was 0.009 g (10%). Found (%): C, 76.20; H, 4.19; N, 5.86. $C_{30}H_{20}N_2O_4$. Calculated (%): C, 76.26; H, 4.27; N, 5.93. IR, ν/cm^{-1}: 1118, 1708, 1732. ^{1}H NMR ($(CD_3)_2CO$), δ: 3.09 (d, 2 H, CH_2, $J = -15.6$ Hz); 3.25 (dd, 2 H, CH_2, $J = -15.6$ Hz, $J = 6.6$ Hz); 5.92 (d, 2 H, CHPh, $J = 6.6$ Hz); 6.25 (s, 2 H, CH=C); 7.23—7.38 (m, 10 H, Ph); 8.12, 8.42 (both s, 1 H each, C_6H_2). ^{13}C NMR, δ: 42.14, 52.16, 103.57, 120.56, 126.13, 128.55, 129.16, 131.21, 133.03, 138.47, 163.67, 166.68, 169.31, 192.20.

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