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INTRAMOLECULAR CYCLIZATION OF 1-[1-ALKYLSULFANYL-2-PHENYL-2-(PHENYLHYDRAZONO)ETHYLIDENE]-PYRROLIDINIUM SALTS

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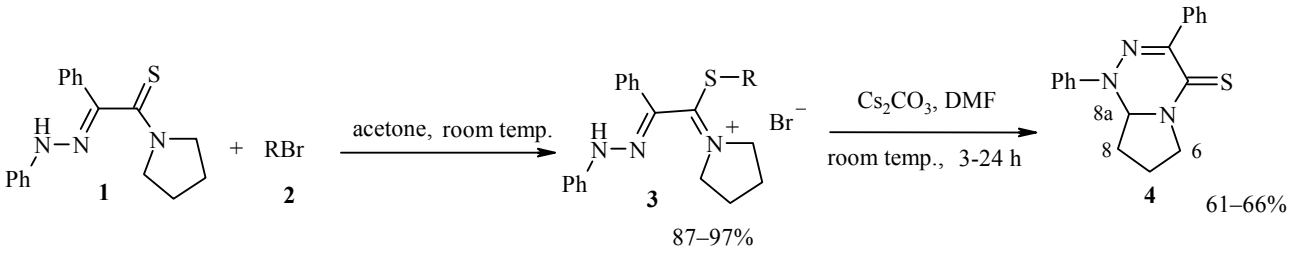
We have discovered that benzyl-, allyl-, and propargylsulfanyl derivatives of pyrrolidinium salts **3** obtained by the alkylation of thioamide **1** in DMF at room temperature in the presence of cesium carbonate may be converted into 1,3-diphenyl-6,7,8,8*a*-tetrahydro-1H-pyrrolo[2,1-*c*]-1,2,4-triazine-4-thione (**4**) in good yields.



2, 3 a R = Bn, **b** R = All, **c** R = propargyl

The use of other organic or inorganic bases such as triethylamine, DBU, and sodium carbonate or other solvents such as acetonitrile leads to an increase in the reaction time and a significant decrease in the yield of thione **4**.

We have previously shown that the intramolecular cyclization of 3-allyl- and 3-propargylsulfanyl-3-(pyrrolidin-1-yl)-2-arylazoacrylonitriles is a new method for the preparation of bicyclic nonaromatic 1,2,4-triazines [1]. The observed transformation of pyrrolidinium salts **3** shows that this reaction is general for alkyl derivatives of arylhydrazonothioacetamides and considerably expands its scope. The products obtained hold practical interest for biological investigation since pyrrolotriazines have high antitumor activity [2].

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The ^1H and ^{13}C NMR spectra were taken on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Varian MAT 311A mass spectrometer with direct sample inlet into the source, accelerating voltage 3 kV, and ionizing electron energy 70 eV.

Synthesis of Alkylsulfanylpyrrolidinium Salts 3a-c (General Method). Alkyl bromide (8.0 mmol) is added to a solution of hydrazone **1** (0.5 g, 1.6 mmol) in acetone (5 ml). The reaction mixture is maintained for 24 h at room temperature. Then, ether is added. The precipitate is filtered off and washed with ether.

1-[1-Benzylsulfanyl-2-phenyl-2-(2-phenylhydrazono)ethylidene]pyrrolidinium Bromide (3b) was obtained in 97% yield; mp 140-141°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.02-2.11 (2H, m, CH_2); 2.18-2.28 (2H, m, CH_2); 3.64-3.76 (2H, m, NCH_2); 4.05-4.11 (2H, m, NCH_2); 4.05 and 4.25 (2H, AB system, J = 14.0, SCH_2); 6.96-7.02 (1H, m, C_6H_5); 7.09-7.16 (5H, m, C_6H_5); 7.31-7.36 (4H, m, C_6H_5); 7.43-7.53 (3H, m, C_6H_5); 7.72 (2H, d, J = 6.8, C_6H_5); 10.62 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 309 $[M\text{-}C_7H_7Br]^+$ (12). Found, %: C 62.32; H 5.37; N 8.66. $C_{25}H_{26}BrN_3S$. Calculated, %: C 62.50; H 5.42; N 8.75.

1-[1-Allylsulfanyl-2-phenyl-2-(2-phenylhydrazono)ethylidene]pyrrolidinium Bromide (3b) was obtained in 87% yield; mp 143-144°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.00-2.46 (4H, m, CH_2); 3.63 (2H, d, J = 6.9, SCH_2); 3.65-3.98 (2H, m, NCH_2); 3.98-4.20 (1H, m, NCH_2); 4.24-4.45 (1H, m, NCH_2); 5.05 (1H, d, J = 10.4, CH_2 allyl); 5.19 (1H, d, J = 16.8, CH_2 allyl); 5.52-5.81 (1H, m, CH allyl); 6.93 (1H, t, J = 6.8, C_6H_5); 7.27 (2H, d, J = 7.8, C_6H_5); 7.33-7.50 (3H, m, C_6H_5); 7.59 (2H, d, J = 7.8, C_6H_5); 7.71 (2H, d, J = 8.2, C_6H_5); 11.09 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 309 $[M\text{-}C_2H_5Br]^+$ (21). Found, %: C 58.54; H 5.51; N 9.67. $C_{21}H_{24}BrN_3S$. Calculated, %: C 58.60; H 5.58; N 9.77.

1-[1-(Prop-2-inylsulfanyl)-2-phenyl-2-(2-phenylhydrazono)ethylidene]pyrrolidinium Bromide (3c) was obtained in 89% yield; mp 150-151°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.02-2.39 (4H, m, CH_2); 2.92 (1H, t, J = 2.4, CH); 3.65-3.93 (2H, m, NCH_2); 3.78 and 3.81 (2H, AB system, J = 17.0, SCH_2); 4.00-4.20 (1H, m, NCH_2); 4.21-4.40 (1H, m, NCH_2); 6.95 (1H, t, J = 7.5, C_6H_5); 7.29 (2H, t, J = 7.6, C_6H_5); 7.38-7.51 (5H, m, C_6H_5); 7.72 (2H, d, J = 8.4, C_6H_5); 11.08 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 309 $[M\text{-}C_3H_3Br]^+$ (18). Found, %: C 58.81; H 4.98; N 9.50. $C_{21}H_{22}BrN_3S$. Calculated, %: C 58.88; H 5.14; N 9.81.

Intramolecular Cyclization of 1-[1-Alkylsulfanyl-2-phenyl-2-(phenylhydrazono)ethylidene]pyrrolidinium Bromides 3a-c (General Method). The Cs_2CO_3 (0.15 g, 0.47 mmol) was added to a solution of pyrrolidinium salt **3a-c** (0.47 mmol) in DMF (5 ml). The reaction mixture was stirred until the starting reagent disappeared as indicated by thin-layer chromatography. The solvent was evaporated in vacuum. Pyrrolotriazine **4** was separated on a column packed with KSK silica gel (40-100 μm) using 4:1 hexane–ethyl acetate as the eluent.

1,3-Diphenyl-6,7,8,8a-tetrahydro-1H-pyrrolo[2,1-*c*]-1,2,4-triazine-4-thione (4), mp 110-111°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.94-2.17 (3H, m, CH_2); 2.61-2.70 (1H, m, CH_2); 3.80-3.98 (2H, m, CH_2); 5.10 (1H, dd, J = 5.8, J = 7.6, H-8a); 7.25-7.38 (4H, m, C_6H_5); 7.39-7.47 (4H, m, C_6H_5); 7.65 (1H, dd, J = 8.0, J = 2.0, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_2), 32.1 (CH_2), 51.5 (CH_2), 71.7 (C(8a)H), 123.2, 126.1, 127.3, 127.9, 128.8, 129.0, 135.3, 144.3, 145.6, 175.8 (CS). Mass spectrum, *m/z* (I_{rel}, %): 307 $[M]^+$ (2). Found, %: C 70.12; H 5.29; N 10.59. $C_{18}H_{17}N_3S$. Calculated, %: C 70.33; H 5.57; N 10.43.

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