Fused polycyclic nitrogen-containing heterocycles
14.* Intramolecular cyclization of 4-azidocarbonyl-2,5-diphenylthiazole. New route to isoquinoline derivatives

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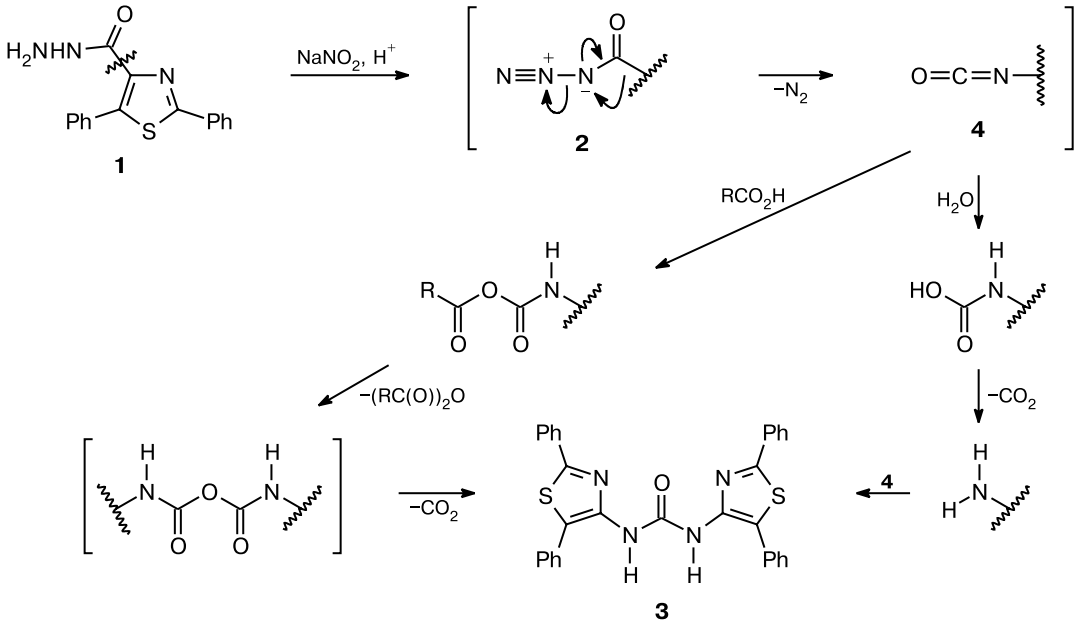
Thermolysis of 2,5-diphenylthiazole-4-carboxylic acid azide is accompanied by intramolecular cyclization to form 2-phenyl-4*H*-thiazolo[4,5-*c*]isoquinolin-5-one through intermediate 2,5-diphenylthiazol-4-yl isocyanate.

Key words: 2,5-diphenylthiazole-4-carboxylic acid, Curtius rearrangement, X-ray diffraction analysis, thiazolo[4,5-*c*]isoquinoline.

Earlier,[2] we have demonstrated that the reaction of sodium nitrite with a solution of hydrazide **1** in acetic or trifluoroacetic acid followed by treatment of the reaction mixture with water afforded not the expected acylazide **2**, but *N*,*N*′-bis(thiazolylurea) **3**. Evidently, this is a consequence of the Curtius rearrangement, which gives initially isocyanate **4** followed by the reaction of the latter with the solvent and water to form urea **3** [3] (Scheme 1). If treatment with water is excluded, the desired 2,5-diphenylthiazole-4-carboxylic acid azide (**2**) can be isolated without impurities of products of its further transformation. This is evidenced by the fact that the IR spectrum shows no absorption bands corresponding to stretching vibrations of free and bound N—H groups. Acylazide **2** is unstable and gradually decomposes at a temperature slightly above the room temperature to form isocyanate **4**, as evidenced by a decrease in the intensity of the $\nu(N_3)$

* For Part 13, see Ref. 1.

Scheme 1



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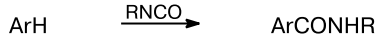
absorption band at 2135 cm^{-1} and the appearance of the ν(N=C=O) band at 2265 cm^{-1}.

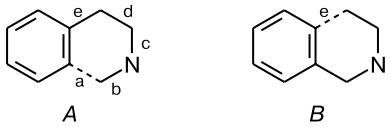
It is known[3] that isocyanates can carbamoylate the aromatic ring (Scheme 2).

Scheme 2



We used this fact to develop a new method for the synthesis of thiazolo[4,5-*c*]isoquinolines starting from readily available thiazolecarboxylic acid hydrazides, in particular, from hydrazide **1**,[4] without isolation of highly reactive intermediate isocyanate **4**.

Most often, the pyridine ring in isoquinolines is formed through the intramolecular electrophilic attack of the C atom of the side chain of correspondingly substituted benzenes on one of the *ortho* positions of the aromatic ring. The ring closure through the pathway *A* involves the attack of the amide C atoms in the Bischler—Napieralski[5] and Pictet—Gams[6] syntheses or the imine C atoms in the Pictet—Spengler synthesis,[7] whereas the ring closure through the pathway *B* involves the attack of the acetal C atoms (the Pomeranz— Fritsch synthesis).[8]



In the case under consideration, the intramolecular reaction leads to the pyridone ring closure of the isoquinolinone system in intermediate isocyanate **4**. The reaction was carried out by heating a solution of azide **2** in diphenyl ether at 250 °C for 2 h (Scheme 3).

Unlike the conventional methods for the construction of the isoquinoline system through the pathway *A*, the electrophilic center in the process under consideration is included in the azatriene system involving the C(4)=C(5) bond of the thiazole ring. Hence, it cannot be ruled out that the thiazoloisoquinoline system is formed as a result of an electrocyclic reaction (Scheme 4).

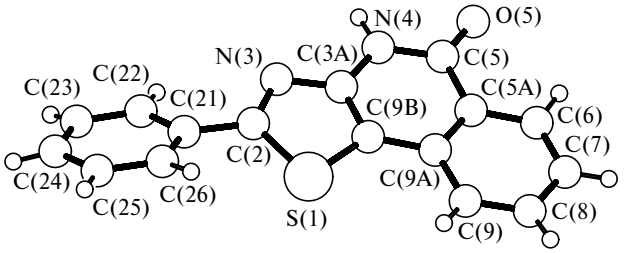


Fig. 1. Molecular structure of thiazolo[4,5-*c*]isoquinoline **5** in the crystal.

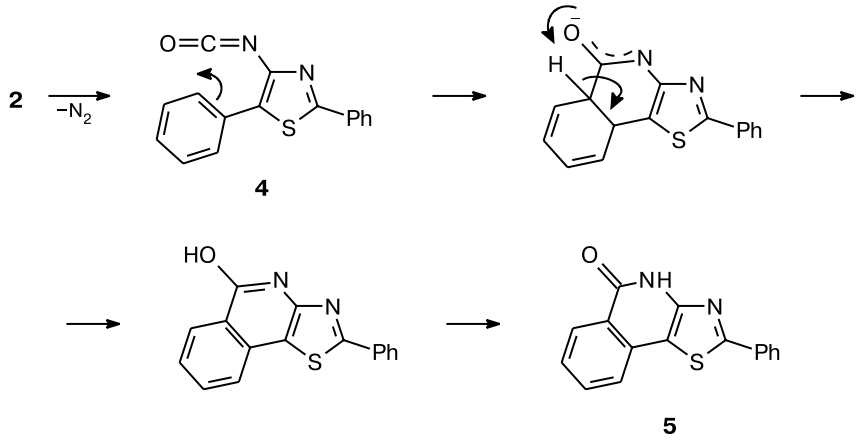
The structure of compound **5** was confirmed by elemental analysis, spectroscopy (IR and ^1H NMR), and X-ray diffraction (Fig. 1). The IR spectrum shows characteristic ν(C=O) and ν(NH) absorption bands at 1650 and 3280—2650 cm^{-1}, respectively. The ^1H NMR spectrum has a broadened singlet of the NH group at low field (δ 12.70) and a doublet for the H(9) proton characteristic of such tricyclic systems[9,10] (δ 8.30, J = 7.76 Hz), which resonates separately from other protons of the benzo fragment. These facts are consistent with the proposed structure of the product.

More prolonged (up to 8 h) but weaker heating (180 °C) of a solution of thiazolylazide **2** in diphenyl ether afforded compound **5** along with another product. The mass spectrum of the latter has a molecular ion peak of the compound with the formula $C_{31}H_{20}N_4S_2$ (found, m/z: $[M]^{\bullet+}$ 512.116; calculated, m/z: $[M]^{\bullet+}$ 512.113).

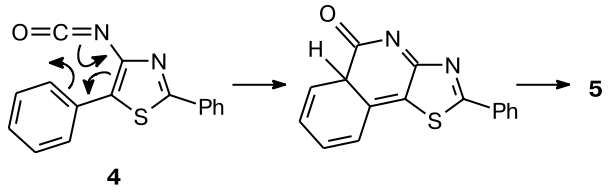
The stoichiometry of the formation of this product from compound **5** can be described by Scheme 5.

The ^1H NMR spectrum of this compound has signals at δ 7.02, 7.15, 7.72, and 7.74 characteristic of the benzo

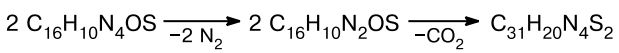
Scheme 3



Scheme 4

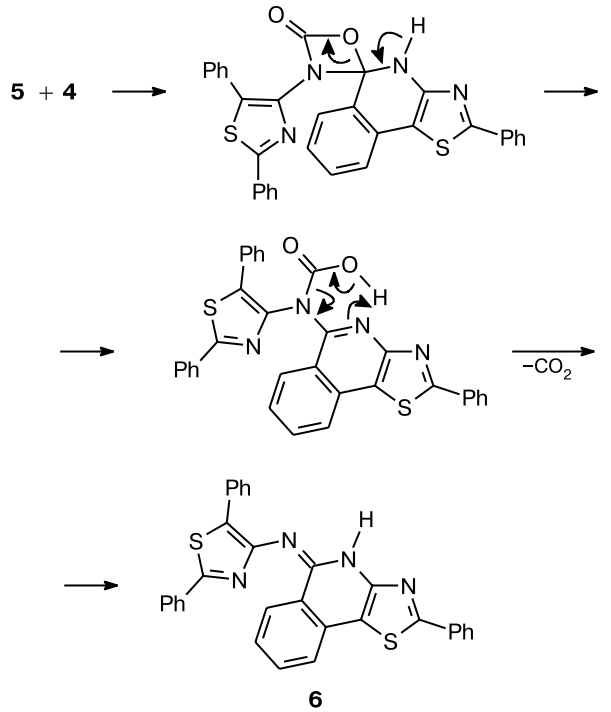


Scheme 5



fragment along with other multiplets (at δ 7.21—7.64 and 8.00—8.17), whose integrated intensities correspond to three phenyl groups, and a broadened singlet (δ 9.77). The IR spectrum shows a band at 3060 cm^{-1} attributable to the bound amide function.[11] Based on these spectroscopic data, we assigned structure **6** to this compound. The formation of the latter is, apparently, attributable to thermal [2+2] cycloaddition of compound **4** to the carbonyl group of thiazoloisoquinolinone **5** through an unstable heterospiro compound, which is typical of isocyanates.[12] Decarboxylation of the latter compound affords final product **6** (Scheme 6).

Scheme 6



Experimental

The melting points were determined on a Boetius hot-stage microscope. The IR spectra were recorded in Nujol mulls on a UR-20 spectrometer. The ^1H NMR spectra were recorded on a Bruker MW-250 spectrometer (250.132 MHz). The mass spectra (EI) were obtained on a MKh-1310 mass-spectrometric complex (R = 1500, ionizing voltage was 70 eV, electron collector current was 30—60 μA, the temperature of external heating of the ion source was 80—200 °C); the sample was introduced *via* a SVP-5 direct inlet probe.

4-Azidocarbonyl-2,5-diphenylthiazole (2). Sodium nitrite (1.4 g, 0.016 mol) was added with stirring to a solution of thiazolecarboxylic acid hydrazide **1** [4] (2.95 g, 0.01 mol) in glacial AcOH (20 mL) at +8 °C under argon. The crystals that precipitated were filtered off and washed with AcOH. Compound **2** was obtained in a yield of 2.6 g (84%), m.p. 240—245 °C (decomp.). Found (%): C, 62.49; H, 3.11; N, 18.36; S, 10.17. $C_{16}H_{10}N_4OS$. Calculated (%): C, 62.75; H, 3.27; N, 18.30; S, 10.47. IR, ν/cm^{-1}: 2135 (N_3), 1695 (C=O), 1675 sh (C=N heteroarom.), 1640 (C=C).

2-Phenyl-4*H*-thiazolo[4,5-*c*]isoquinolin-5-one (5). A solution of azide **2** (1.53 g, 5 mmol) in diphenyl ether (10 mL) was stirred under dry argon at 250 °C (bath temperature) for 2 h. After cooling, the reaction mixture was diluted with isopropyl alcohol (5 mL) and allowed to stand. The crystals that precipitated were filtered off, dried in air, and recrystallized from Pr^iOH. Compound **5** was obtained in a yield of 0.9 g (65%), m.p. 256—260 °C. Found (%): C, 69.21; H, 3.37; N, 10.24; S, 11.50. $C_{16}H_{10}N_2OS$. Calculated (%): C, 69.07; H, 3.59; N, 10.07; S, 11.52. IR, ν/cm^{-1}: 3280—2850 (NH), 1650 (C=O), 1607 (C=N). ^1H NMR (CD_3OD), δ: 7.52 (br.s, 5 H, Ph); 7.66 (br.s, 1 H, H(6)); 7.92—7.99 (m, 2 H, H(7), H(8)); 8.30 (d, 1 H, H(9), J = 7.76 Hz); 12.70 (br.s, 1 H, NH).

5-(2,5-Diphenylthiazol-4-yl)imino-2-phenyl-4*H*-thiazolo[4,5-*c*]isoquinoline (6). A solution of azide **2** (1 g, 3.27 mmol) in diphenyl ether (10 mL)) was stirred under dry argon at 180 °C (bath temperature) for 8 h and then allowed to stand for ~12 h. The crystals that precipitated were filtered off, washed with isopropyl alcohol (3×5 mL), and dried in air. Compound **6** was obtained in a yield of 0.45 g (54%), m.p. 280—283 °C. Found (%): C, 72.69; H, 3.87; N, 10.74; S, 12.56. $C_{31}H_{20}N_4S_2$. Calculated (%): C, 72.65; H, 3.90; N, 10.94; S, 12.51. IR, ν/cm^{-1}: 3070 (NH), 1615, 1595, 1570 (C=N heteroarom.). ^1H NMR (CD_3OD), δ: 7.02 (d, 1 H, H(6) or H(9), J = 7.19 Hz); 7.72 (d, 1 H, H(9) or H(6), J = 7.22 Hz); 7.74 (dd, 1 H, H(7) or H(8), J = 7.19 Hz, J = 7.22 Hz); 7.15 (dd, 1 H, H(8) or H(7), J = 7.19 Hz, J = 7.22 Hz); 7.21—7.64 (m, 9 H, H arom.); 8.00—8.17 (m, 6 H, H arom.); 9.77 (br.s, 1 H, NH). Cooling of the filtrate afforded crystals, which were filtered off, washed with Pr^iOH (5 mL), and dried in air. Thiazoloisoquinoline **5** was obtained in a yield of 0.2 g (22%).

X-ray diffraction study of compound 5 was performed on an automated four-circle Enraf-Nonius CAD-4 diffractometer. Crystals of compound **5** ($C_{16}H_{10}N_2OS$) are orthorhombic, at 20 °C a = 14.258(1) Å, b = 7.218(2) Å, c = 25.611(5) Å, V = 2636(1) $Å^3$, Z = 8, d_{calc} = 1.40 g cm^{-3}, space group *Pbca*. The unit cell parameters and the intensities of 2763 reflections, of which 1199 reflections were with $I \geq 2\sigma$, were measured at 20 °C (λ(Mo-Kα), graphite monochromator, ω/2θ scanning tech-

nique). The structure was solved by direct methods using the SIR program[13] and refined first isotropically and then anisotropically. All calculations were carried out using the MolEN program package[14] on an AlphaStation 200. The molecular structure was drawn and intra- and intermolecular interactions were calculated using the PLATON program.[15]

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