Hydrazinolytic recyclization of 2-phenacylbenzothiazole

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Hydrazinolytic recyclization of 2-phenacylbenzothiazole proceeds *via* cleavage of the C—S bond in the ring and is accompanied by oxidation of resulting 2-[(5-phenylpyrazole-3-yl)amino]thiophenol into the corresponding disulfide. The subsequent intramolecular cyclocondensation gives selectively pyrazolo[4,3-*b*][1,4]benzothiazines.

Key words: 1,4-benzothiazines, benzothiazoles, hydrazines, hydrazones, disulfides, oxidation, pyrazoles, recyclization, spiranes, cyclocondensation.

Recyclizations are unique as regards the scope of synthesis of functionalized compounds; however, they have substantial limitations, as they are fairly sensitive to the stability of the starting ring and the effect of substituents.[1—6] According to our data,[7] 2-phenacyl-1*H*-benzimidazole undergoes hydrazinolytic recyclization with substantial difficulty. It reacts with hydrazines to give rather stable hydrazones whose tendency to undergo recyclization to give pyrazole derivatives sharply decreases in the presence of substituents at the amino group of the hydrazone fragment. The limitations of this recyclization can be overcome by conducting the process under acylation reaction conditions, because the acylating reagent can be selectively directed on the benzimidazole ring nitrogen atom, which destabilizes the ring and induces an intramolecular rearrangement.

Previously, we reported[8] that 2-phenacylbenzothiazole (**1**) reacts with hydrazines somewhat differently from the benzimidazole analog. Indeed, only the reaction with 4-nitrophenylhydrazine does form the corresponding hydrazone **2**. In the case of β-hydroxyethylhydrazine, the reaction gives enehydrazine **3**, which exists in solution in equilibrium with the tautomeric spiro form **3′**. The reaction with hydrazine with refluxing in propan-2-ol for 1 h gives relatively stable spiro compound **4**. This work continues the study in order to find transformations caused by the possible rearrangement of the benzothiazole core.

It was found (Scheme 1) that spirane **4** undergoes opening of the thiazole ring at the C—S bond in dioxane even at 20—25 °C. However, this transformation cannot be stopped after the formation of the expected thiol **5**, because it is readily oxidized under the experimental conditions to give disulfide **6**, which was isolated from the reaction mixture. Disulfides of a similar structure formed in the reaction of *o*-aminothiophenol with 1,3-dicarbonyl compounds are known[9] to easily undergo oxidative cyclocondensation to 1,4-benzothiazine derivatives on heating to 150 °C in dimethyl sulfoxide. According to our data, compound **6** is converted into 2,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine **7** under the same conditions through an intramolecular electrophilic attack by a disulfide sulfur atom on the electron-enriched position of the 4 pyrazole ring.

By using phenylhydrazine in the reaction with compound **1**, one can obtain disulfide **8** or, by conducting the reaction further, it is possible to bring it to the formation of 1,3-diphenyl-1,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine (**9a**) (Scheme 2). Compound **8** is formed on long-term keeping of the reactants in ethanol with the access of air oxygen, while **9a** is produced on heating in a mixture of acetic acid with dimethyl sulfoxide. *p*-Nitrophenylhydrazone **2** and enehydrazine **3** are also capable of hydrazinolytic recyclization accompanied by oxidative cyclocondensation. On heating with dimethyl sulfoxide, they are selectively converted into pyrazolobenzothiazines **9b,c**.

The composition and structure of the resulting compounds were confirmed by elemental analysis (Table 1) and ^{1}H NMR (Table 2).

Comparison of the ^{1}H NMR of disulfides **6** and **8** allows one to identify essential differences in the structure of their molecules. It should be borne in mind that the N—Ph substituents in compound **8** can act as an additional factor affecting the chemical shifts. Therefore, only those changes that can be attributed mainly to the deshielding effect of the pyridine-type pyrazole nitrogen atom on the closest environment are taken into account. This effect is most pronounced for the *o*-protons of the C—Ph substituents in compound **8** and aniline fragments of compound **6**. Correspondingly, the *o*-protons of the C-phenyl substituents of compound **6** resonate at 7.72 ppm and those in **8** resonate in a lower field, at 7.91 ppm. The

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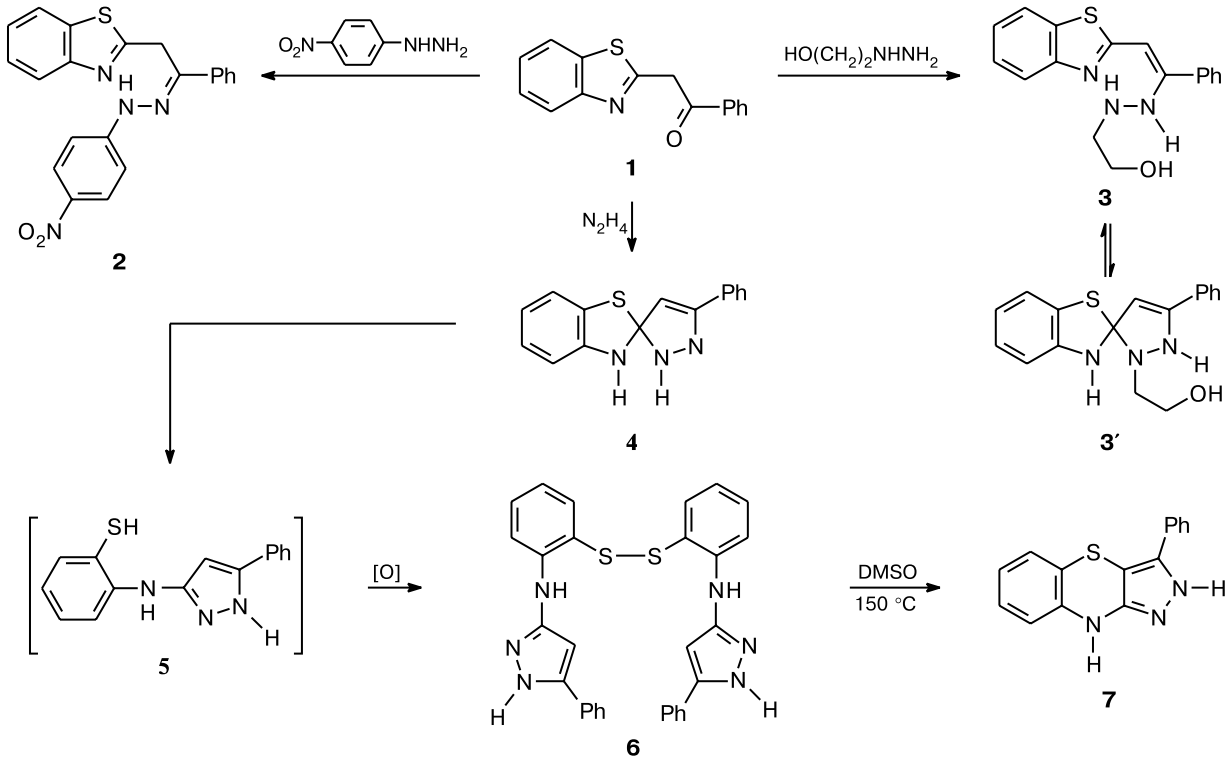
Scheme 1



Scheme 2

9: R = Ph (**a**), 4-$NO_2C_6H_4$ (**b**), $(CH_2)_2OH$ (**c**)

difference is more pronounced for the *o*-protons of the aniline fragments, which occur at 7.88 ppm for compound **6** and in a higher field, at 7.03 ppm, for compound **8**. As have been reported in our previous study,[10] this difference between 3- and 5-anilinopyrazoles is typical and can provide grounds for confirming their structure. It is also noteworthy that compound **6** does not tend to transfer the proton between the nitrogen atoms of the pyrazole ring to be converted into isomeric structure **8**. This conclusion follows from the fact that no doubling of signals is observed in the spectrum. The structure of **6**, unlike **8**, has a shorter system of conjugation between the endocyclic amino group and the pyrazole azomethine bond, which may be responsible for its energetic stabilization.

In pyrazolobenzothiazine **7**, no proton transfer between the nitrogen atoms of the pyrazole ring to give isomeric structure **9** is observed either. The phenyl

Table 1. Yields, elemental analysis data, and melting points of the compounds

Compound	Yield (%)	M.p. /°C (decomp.)	Found / Calculated (%)			Molecular formula
			C	H	N	
6	85	223—225	67.56 67.64	4.45 4.54	15.76 15.78	$C_{30}H_{24}N_6S_2$
7	84	185—187	67.82 67.90	4.08 4.18	15.75 15.84	$C_{15}H_{11}N_3S$
8	72	120—121.5	73.47 73.66	4.58 4.71	12.16 12.27	$C_{42}H_{32}N_6S$
9a	89	151—153	73.71 73.87	4.54 4.43	12.19 12.31	$C_{21}H_{15}N_3S$
9b	97	225—227	65.37 65.27	3.48 3.65	14.39 14.50	$C_{21}H_{14}N_4O_2S$
9c	94	145—147	65.88 66.00	4.79 4.89	13.45 13.58	$C_{17}H_{15}N_3OS$

substituent in the molecule is removed from the azomethine bond of the pyrazole ring and experiences little electron-withdrawing and deshielding influence and, hence the signal for the *o*-protons occurs at 7.55 ppm and almost overlaps with the signal for the *m*-protons at 7.50 ppm. Conversely, in compounds **9a—b**, the influence of the pyrazole azomethine bond on the Ph(C) substituent is much more pronounced due to their spatial proximity. In these examples, the signals for the Ph(C) *o*-protons are shifted downfield by 0.18—0.22 ppm with respect to the signals for the *m*-protons and occur at 7.60—7.70 ppm.

The difference between the signals for the aromatic protons of the N—Ph substituent in disulfide **8** and pyrazolobenzothiazine **9a** deserves attention. In the former case, the *o*-protons resonate in lower field (7.74 ppm) than the *m*-protons due to the deshielding effect of the pyrazole ring. In the latter case, the *o*- and *m*-protons are responsible for a common narrow multiplet at 7.59—7.60 ppm, indicating that the N—Ph group cannot be located in one plane with the pyrazole ring due to the spatial hindrance from the proton of the amino group of the benzothiazine fragment.

Comparison of the mass spectra of spirane **4**, disulfide **6**, and pyrazolobenzothiazine **7** (Table 3) provides information on the details of the 1,4-benzothiazine ring closure. The spectrum of compound **6** represents an overlap of the spectra of compounds **4** and **7**. Hence, the disulfide easily cyclizes under conditions of recording the spectra to give pyrazolobenzothiazine **7** with elimination of spirane **4** or isomeric (pyrazolylamino)thiophenol **5** (or their mixture). In the above-mentioned synthesis of compound **7** from disulfide **6**, dimethyl sulfoxide functions as an oxidant, which promotes complete transformation of the intermediates into the final product.

Note that only two pyrazolo[4,3-*b*][1,4]benzothiazine derivatives have been reported. One has been prepared by cyclocondensation of 3-chloro-2-formyl[1,4]benzothiazine with *p*-chlorophenylhydrazine,[11] while the other, by oxidative cyclocondensation of 2-benzoyl-4-methyl[1,4]benzothiazine with hydrazine.[12]

Thus, we developed a new preparatively convenient and efficient method for the synthesis of pyrazolo[4,3-*b*][1,4]benzothiazine based on hydrazinolytic recyclization of 2-phenacylbenzothiazole followed by intramolecular oxidative cyclocondensation. In addition, it was found that the benzothiazole ring is much more prone to recyclization than the benzimidazole ring.

Table 2. ^{1}H NMR data for the synthesized compounds

Compound	δ (*J*/Hz)
6	6.38 (s, 2 H, H(4′)); 6.71 (m, 2 H, H(4)); 7.25 (d, 2 H, H(6), *J* = 7.8); 7.27—7.38 (m, 4 H, H(5) + H_{Ph}(4)); 7.46 (m, 4 H, H_{Ph}(3), H_{Ph}(5)); 7.65 (s, 2 H, NH — subject to deuterium exchange); 7.72 (d, 4 H, H_{Ph}(2), H_{Ph}(6), *J* = 7.8); 7.88 (d, 2 H, H(3), *J* = 6.6); 12.71 (s, 2 H, H(1′) — subject to deuterium exchange)
7	6.64—6.96 (m, 4 H, H(5), H(6), H(7), H(8)); 7.34—7.39 (m, 1 H, H_{Ph}(4)); 7.47—7.52 (m, 2 H, H_{Ph}(3), H_{Ph}(5)); 7.55 (d, 2 H, H_{Ph}(2), H_{Ph}(6), *J* = 7.2); 8.81 (s, 1 H, H(9)); 12.37 (s, 1 H, H(2))
8	6.66 (m, 2 H, H(4)); 6.72 (d, 2 H, H(6), *J* = 7.8); 6.74 (s, 2 H, H(4′)); 7.03 (d, 2 H, H(3), *J* = 7.8); 7.18 (m, 2 H, H(5)); 7.27—7.48 (m, 12 H, H_{NPh}(3), H_{NPh}(4), H_{NPh}(5) + H_{CPh}(3), H_{CPh}(4), H_{CPh}(5)); 7.74 (d, 4 H, H_{NPh}(2), H_{NPh}(6), *J* = 7.2); 7.91 (d, 4 H, H_{CPh}(2), H_{CPh}(6), *J* = 7.2); 7.94 (s, 2 H, NH)
9a	6.78—6.99 (m, 4 H, H(5), H(6), H(7), H(8)); 7.35—7.40 (m, 1 H, H_{CPh}(4)); 7.45—7.50 (m, 3 H, H_{CPh}(3), H_{CPh}(5) + H_{NPh}(4)); 7.59—7.60 (m, 4 H, H_{NPh}(2), H_{NPh}(3), H_{NPh}(5), H_{NPh}(6)); 7.69 (d, 2 H, H_{CPh}(2), H_{CPh}(6)); 8.56 (c, 1 H, H(9))
9b	6.79—7.03 (m, 4 H, H(5), H(6), H(7), H(8)); 7.39—7.44 (m, 1 H, H_{Ph}(4)); 7.47—7.52 (m, 2 H, H_{Ph}(3), H_{Ph}(5)); 7.70 (d, 2 H, H_{Ph}(2), H_{Ph}(6), *J* = 8.4); 7.92 and 8.42 (both d, 2 H each, *p*-C_6H_4, *J* = 9.0); 8.75 (s, 1 H, H(9))
9c	3.71—3.77 (m, 2 H, CH_2O); 4.08 (t, 2 H, CH_2N, *J* = 5.7); 5.00 (t, 1 H, OH, *J* = 4.8); 6.74—6.98 (m, 4 H, H(5), H(6), H(7), H(8)); 7.28—7.33 (m, 1 H, H_{Ph}(4)); 7.39—7.44 (m, 2 H, H_{Ph}(3), H_{Ph}(5)); 7.60 (d, 2 H, H_{Ph}(2), H_{Ph}(6), *J* = 7.5); 8.57 (s, 1 H, H(9))

Table 3. Data of mass spectra of compounds **4**, **6**, and **7**

Compound	m/z (I_{rel} (%))
4	267 (100) $[M^+]^a$, 236 (13), 234 (25), 164 (15), 131 (16), 119 (14), 104 (13), 77 (21)
6	267 (61) $[M^+]^b$, 265 (100) $[M^+]^b$, 236 (27), 234 (18), 164 (12), 135 (20), 131 (15), 104 (14), 77 (23)
7	265 (100) $[M^+]^c$, 236 (10), 135 (13), 133 (17), 104 (6), 77 (6)

[a] $C_{15}H_{13}N_3S$. Calculated, M = 267.
[b] $C_{30}H_{24}N_6S_2$. Calculated, M = 532.
[c] $C_{15}H_{11}N_3S$. Calculated, M = 265.

Experimental

^{1}H NMR spectra were recorded on a Varian VXR-300 instrument (300 MHz) in DMSO-d_6 using Me_4Si as the internal standard. Mass spectra were recorded on an MX 1321 instrument under standard conditions (EI, 70 eV). The reactions were monitored and the purity of the synthesized compounds was checked by TLC on Silufol-254 plates in a 99 : 1 benzene—ethanol mixture; the plates were visualized in the UV light. The melting points were measured in sealed capillaries and were not corrected. The physicochemical characteristics of the products are presented in Table 1.

Di[2-(5-phenylpyrazol-3-ylamino)phenyl] disulfide (6). A mixture of compound **4** (0.534 g, 2 mmol) and 4.0 mL of dioxane was heated until a homogeneous solution formed, which was stirred for 24 h at 20—25 °C. Water (2.0 mL) was added and the mixture was heated to boiling. After cooling, the yellow precipitate was filtered off, washed by propan-2-ol, and crystallized from a 2 : 1 dioxane—water mixture.

3-Phenyl-2,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine (7). A mixture of compound **6** (0.266 g, 0.5 mmol) and 1.0 mL of dimethyl sulfoxide was kept for 3 h at 145—150 °C. Water (1.5 mL) was added and the mixture was stirred. After cooling, the orange-red precipitate was filtered off, washed with a 1 : 1 propan-2-ol—water mixture and crystallized from a 2 : 1 propan-2-ol—water mixture.

Di[2-(1,3-diphenylpyrazol-5-ylamino)phenyl] disulfide (8). A mixture of compound **1** (0.506 g, 2 mmol), phenylhydrazine (0.238 g, 2.2 mmol), and 1 mL of glacial acetic acid was kept for 30 min at 55—60 °C. Water (5.0 mL) was added and the mixture was stirred. The aqueous layer was decanted and the remaining oil was dissolved in 15 mL of ethanol and kept for 48 h at 20—25 °C in an open vessel. The yellow precipitate that formed was filtered off, washed with propan-2-ol, and crystallized from a 5 : 1 propan-2-ol—acetone mixture.

1,3-Diphenyl-1,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine (9a). A mixture of compound **1** (0.506 g, 2 mmol), phenylhydrazine (0.238 g, 2.2 mmol), and 1 mL of glacial acetic acid was stirred for 20 min at 55—60 °C, diluted with dimethyl sulfoxide (0.624 g, 8 mmol), and kept for 3 h at 85—90 °C. Water (1.0 mL) was added and the mixture was heated to boiling with stirring. After cooling, the orange-red precipitate was filtered off, washed with propan-2-ol, and crystallized from an 1 : 1 ethyl acetate—propan-2-ol mixture.

1-(4-Nitrophenyl)-3-phenyl-1,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine (9b). A mixture of compound **2** (0.388 g, 1 mmol), dimethyl sulfoxide (0.312 g, 4 mmol), and 1.0 mL of glacial acetic acid was kept for 1 h at 85—90 °C. After cooling, the violet-red precipitate was filtered off, washed with propan-2-ol, and crystallized from a 2 : 1 pyridine—water mixture.

1-(2-Hydroxyethyl)-3-phenyl-1,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine (9c). A mixture of compound **3** (0.311 g, 1 mmol) and 0.5 mL of dimethyl sulfoxide was kept for 1 h at 130—140 °C. Water (0.5 mL) was added and the mixture was stirred. After cooling, the orange-red precipitate was filtered off, washed with a 1 : 1 propan-2-ol—water mixture, and crystallized from a 2 : 1 propan-2-ol—water mixture.

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