Synthesis of 6-phenyl and 6-styrylthiazolo[3,2-*b*][1,2,4]triazoles

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Thiazole rings have been often encountered in the structure of antibiotic or antitumor drugs. An easy synthesis of them has revealed itself necessary in order to elucidate the mechanism of action of these naturally occurring substances. A method of preparation of conjugated b-ethylenic thiazole[3,2-*b*][1,2,4]triazoles by heating a 3-thio substituted [1,2,4]triazole in the presence of polyphosphoric acid is reported here, giving the expected product in a 60% yield.

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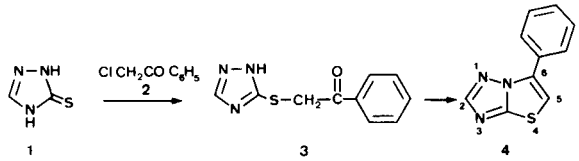
Some naturally occurring substances of pharmacological interest have been found to possess a thiazole ring in their structure. The exact role of this heterocycle in the mode of action of antibiotic or antitumor drugs such as thiostrepton [1], dysidenin [2], ulicyclamide [3], dolastatin [4] or patellamide [5] remains obscure. We have recently proposed synthetic methods for the preparation of key thiazolyl intermediates [6] and simplified models of thiazole ring-containing cyclic peptides [7]. These thiazole derivatives can be considered as useful tools for the study of the mechanism of action of the recently isolated marine peptides [2-5]. We used the same technique - small models design - to study the exact role of the thiazole part of the well-known antitumor bleomycin in binding of the drug to DNA [8]. We concluded that the thiazole moiety wedges in between the base pairs at bends in a kinked DNA. A full overlap of base pairs is not allowed, considering the small aromatic surface of the bleomycin bithiazole. To improve the aromatic rings stacking by a best overlap of the DNA bases, we propose here the synthesis of a condensed thiazole ring, a thiazolo[3,2-*b*]-*s*-triazole substituted by a phenyl or a styryl group.

Synthesis.

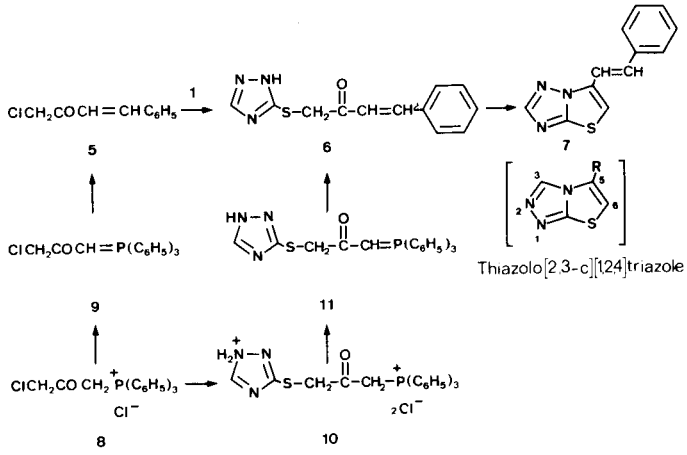
Cyclization of 3-phenacylthio[1,2,4]triazole **3** to 6-phenylthiazolo[3,2-*b*][1,2,4]triazole **4** was obtained by heating in the presence of polyphosphoric acid. The intermediate compound **3** was easily prepared by the reaction of phenacyl bromide **2** with [1,2,4]triazoline-3-thione in boiling ethanol (Scheme 1).

Scheme 1



6-Styrylthiazolo[3,2-*b*][1,2,4]triazole **7** was obtained using a similar two-step pathway involving the initial condensation of triazolinethione **1** with chloromethyl styryl ketone **5**. This unsaturated chloromethyl ketone was prepared starting from (3-chloro-2-oxo)propyltriphenylphosphonium chloride **8** [9]. The corresponding Wittig reagent triphenylchloroacetonylphosphorane **9** reacted easily with benzaldehyde to give chloromethyl styryl ketone **5** in a good yield (Scheme 2).

Scheme 2



Discussion.

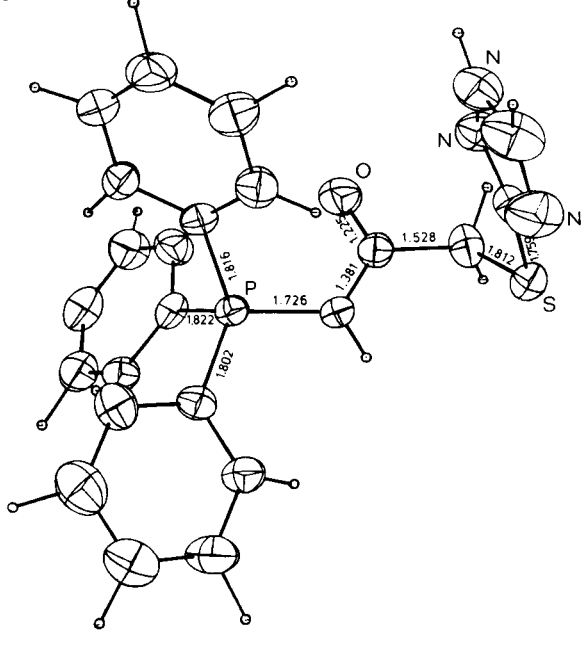
Owing to the annular tautomerism of the triazolinethione ring, the intramolecular cyclization of thiomethyl ketones such as **3** or **6** can involve a dehydration between the carbonyl group and either N_1 or N_4 protonated nitrogen atom, leading to the formation of thiazolo[3,2-*b*]-[1,2,4]triazole or thiazolo[2,3-*c*][1,2,4]triazole respectively. The cyclization appears to be sensitive to the acidity and polarity of the medium and influenced by the temperature [10,11].

The reaction conditions have a considerable influence on the basicity of N_1 or N_4. Under thermal conditions, in

the presence of polyphosphoric acid such as in the experiments described here, the more basic center is undoubtedly associated with N_1 and cyclizations of **3** and **6** lead to 6-phenyl and 6-styrylthiazolo[3,2-*b*][1,2,4]triazole. Concerning the later compound, an unequivocal method has been recently described [12] to prepare the 5-styrylthiazolo[2,3-*c*][1,2,4]triazole isomer.

In order to generalize the method of preparation of conjugated 6-ethylenic thiazolo[3,2-*b*][1,2,4]triazoles, we have synthetized a phosphonium salt **10** and the corresponding phosphorus ylid **11**. This compound has been used to prepare the compound **6** by the Wittig reaction. But the above described cyclization in the presence of polyphosphoric acid curiously failed when applied directly to the phosphorane **11**. Other attempts to form the fused bicyclic thiazolotriazole from the phosphorane **11** either in acidic or basic conditions also failed. This lack of reaction is understandable in terms of the influence of the phosphorus ylid on the electronegativity of the carbonyl group.

On the other hand, the cyclization is not favored as demonstrated by the structural analysis of the phosphorane. In the solid state, this molecule exhibits an important electronic delocalization along the ylid moiety P-C-C-O which induces a structural rigidity. The plane formed by these four atoms is nearly perpendicular to the plane of the triazole ring: these two planes stand at an angle of 83°. The hydrogen atoms have been located without ambiguity and the NH proton of the triazole ring is at the 1-position, the side chain being at the 3-position. Thus the relative positions in the space of the potential reactive sites for the cyclization (the side chain carbonyl and the heterocyclic NH) are not favorable to the formation of either thiazolo[3,2-*b*][1,2,4]triazole or thiazolo[2,3-*c*][1,2,4]triazole (see Figure).



EXPERIMENTAL

Melting points were taken on a Tottoli melting-point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 177 infrared-spectrometer using potassium bromide pellets. The ^{1}H nmr spectra were recorded on a Jeol JNM-MH 60 and on a Perkin-Elmer 90 MHz spectrometer. The chemical shifts are in ppm using tetramethylsilane as internal standard. Microanalyses were performed with a Perkin Elmer CHN 240.

3-Phenacylthio[1,2,4]triazole **3**.

A solution of [1,2,4]triazoline-3-thione **1** (5 g, 0.05 mole) in ethanol was added to a solution of chloroacetophenone **2** (7.7 g, 0.05 mole) in ethanol and the mixture stirred under reflux for 2 hours and at room temperature for 12 hours. The precipitated product was filtered and recrystallized from water to give 3-phenacylthio[1,2,4]triazole **3** in 89% yield, mp 121°; ir: 1690 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 10.96 (s, 1H, triazole ring NH, exchangeable by deuterium oxide), 8.40 (s, 1H, triazole ring CH), 7.57-8.00 (m, 5H, phenyl protons), 4.82 (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.79; H, 4.11; N, 19.17. Found: C, 54.07; H, 4.28; N, 19.08.

6-Phenylthiazolo[3,2-*b*][1,2,4]triazole **4**.

3-Phenacylthio[1,2,4]triazole **3** (2 g) and polyphosphoric acid (8 g) were heated at 160° for 3 hours. Then an aqueous solution of sodium hydrogen carbonate was added and the crude product was extracted twice by ethyl acetate. The extracts were washed with water and dried over anhydrous sodium sulfate. After removing of the solvent under reduced pressure, the residue was crystallized from petroleum ether to give 6-phenylthiazolo[3,2-*b*][1,2,4]triazole in a 61% yield, mp 80°; ir: 1550 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ 8.50 (s, 1H, 2-CH), 7.65-7.50 (m, 5H, phenyl), 7.66 (s, 1H, 5-CH).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.53; H, 3.53; N, 20.81.

Chloromethyl Styryl Ketone **5**.

Triphenylchloroacetonylphosphorane **9** [9] (7.05 g, 0.02 mole) was added to benzaldehyde (10.6 g, 0.1 mole) and the mixture was stirred at 80° for 72 hours. After completion of the reaction, excess of benzaldehyde was removed and cyclohexane was added to the residue. The precipitated phosphine oxide was filtered. After evaporation of the solvent, the residue was distilled ($bp_{0.01}$ = 114°) to give a white solid product by cooling, 42% yield, mp 62°; ir: 1690 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 7.80 -7.42 (m, 5H, phenyl), 7.68 (d, 1H, ethylenic CH, J = 15 Hz), 7.02 (s, 1H, ethylenic CH, J = 15 Hz), 4.87 (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_9ClO$: C, 66.48; H, 4.99. Found: C, 66.52; H, 5.03.

3-[4-(1-Phenyl-3-oxobutenyl)thio][1,2,4]triazole **6**.

A solution of [1,2,4]triazoline-3-thione **1** (1 g, 0.01 mole) in ethanol was added to a solution of chloromethyl styryl ketone **5** (1.8 g, 0.01 mole) in ethanol. After heating under reflux for 2 hours and stirring for 12 hours at room temperature, the precipitated product was filtered and recrystallized from ethanol to yield the expected compound **6** in 72% yield, mp 137°; ir: 1690 cm^{-1} (conjugated CO); ^{1}H nmr (DMSO-d_6): δ 9.00 (s, 1H, NH), 8.71 (s, 1H, triazole ring CH), 7.80 (d, 1H, ethylenic CH, J = 15 Hz), 7.38-7.85 (m, 5H, phenyl), 7.12 (d, 1H, ethylenic CH, J = 15 Hz), 4.60 (s, 2H, CH_2).

Anal. Calcd. for $C_{12}H_{11}N_3OS$: C, 58.78; H, 4.49; N, 17.14. Found: C, 58.70; H, 4.55; N, 17.19.

6-Styrylthiazolo[3,2-*b*][1,2,4]triazole **7**.

The above compound **6** (0.5 g) and polyphosphoric acid were heated at 160° for 3 hours. After neutralization by sodium hydrogen carbonate, extraction by ethyl acetate, washing with water, drying over sodium sulfate and evaporation of the solvent, the white powder was recrystallized from ethanol to give 6-styrylthiazolo[3,2-*b*][1,2,4]triazole **7** in a 54% yield, mp 114°; ir: 1550 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ 8.42 (s, 1H, 2-CH), 8.03 (d, 1H, ethylenic CH, J = 15 Hz), 7.62 (s, 1H, 5-CH), 7.37 (d, 1H, ethylenic CH, J = 15 Hz), 7.68-7.16 (m, 5H, phenyl).

Anal. Calcd. for $C_{12}H_9N_3S$: C, 63.44; H, 3.96; N, 18.50. Found: C, 63.32; H, 4.01; N, 18.61.

3-[3-(2-Oxopropyl)thio][1,2,4]triazolyltriphenylphosphonium Chloride Hydrochloride **10**.

A solution of [1,2,4]triazoline-3-thione **1** (10 g, 0.1 mole) and (3-chloro-2-oxo)propyltriphenylphosphonium chloride **8** [9] (40 g, 0.1 mole) in ethanol was stirred under reflux for 3 hours. The expected product precipitated during the course of the reaction as small white crystals, yield 95%, mp 195°; ir: 1745 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 11.41 (s, 2H, NH_2^+), 8.60 (s, 1H, triazole ring CH), 7.60 (m, 15H, phenyl protons), 6.00 (d, 2H, P-CH_2, J_{P-H} = 12 Hz), 4.47 (s, 2H, CH_2-S).

Anal. Calcd. for $C_{23}H_{22}Cl_2N_3OPS$: C, 55.87; H, 4.49; N, 8.50. Found: C, 54.84; H, 4.50; N, 8.16.

3-(Triphenylphosphoraneacetonylidenethio)[1,2,4]triazole **11**.

The phosphonium salt **10** was easily converted to the corresponding phosphorane **11** by the action of sodium ethylate in ethanol, mp 218°; ir: 1530 cm^{-1}; ^1H nmr (deuterated acetic acid): δ 8.37 (s, 1H, triazole ring CH), 7.67 (s, 15H, phenyl protons), 7.60 (s, 1H, CH).

Anal. Calcd. for $C_{23}H_{20}N_3OPS$: C, 66.17; H, 4.83; N, 10.07. Found: C, 65.92; H, 4.77; N, 10.00.

Pale yellow single crystals of phosphorane **11** were obtained by solvent evaporation in the cold from an ethanolic solution.

Crystal data (MoKα = 0.7107 A): monoclinic, a = 9.731(18)A, b = 8.306(17)A, c = 28.375(40)A, β = 115.87°, space group $P2_{1/C}$.

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