The Reaction of 3,5-Diphenyl-1,2,4-dithiazol-1-ium Perchlorate with Active Methylene Compounds

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Synopsis. The reaction of 3,5-diphenyl-1,2,4-dithiazol-1-ium perchlorate with several kinds of active methylenes gives a number of heterocycles, such as 4-hydroxy and 4-mercaptopyrimidine, pyrimidinone, and thiazole derivatives. On treatment with hydroxylamine-*O*-sulfonic acid, the 4-mercaptopyrimidines lead to the aminothio compounds or the isothiazolo[5,4-*d*]pyrimidine.

Some heteroaromatic cationic species have high reactivity against nucleophiles, such as amino compounds and various kinds of carbanions.[1] The reactivities of heteroaromatic cations are essentially similar, but, strictly speaking, they react with a nucleophile in slightly different fashions to lead to various types of derivatives.[2] 3,5-Diphenyl-1,2-dithiol-1-ium cation was found to react with active methylenes to produce a number of derivatives.[3] It can therefore be assumed that 3,5-diphenyl-1,2,4-dithiazol-1-ium cation, the *N*-analog of the corresponding dithiolium cation, would afford several derivatives by treatment with active methylenes. In the present study, the reaction of 3,5-diphenyl-1,2,4-dithiazol-1-ium perchlorate (**1**) with several active methylene compounds was carried out in order to survey its reactivity.

The starting material, **1**, was obtained by treating thiobenzamide with thiobenzanilide *S*-oxide in acetic anhydride–perchloric acid.[4]

When cyanoacetamide, benzoylacetamide, and benzoylacetoanilide were heated to reflux with **1** in MeO-Na–MeOH, **2**, **3**, and **4** were afforded in 92, 38, and 44% yields respectively. These were same compounds given by the reaction of 2,4,6-triphenyl-1,3,5-thiadiazin-1-ium salt with these reagents,[5] so that **2**, **3**, and **4** were identified to be 5-cyano- and 5-benzoyl-4-hydroxy-2,6-diphenylpyrimidine, and 5-benzoyl-2,3,6-triphenyl-4(3*H*)-pyrimidinone. 3,5-Diphenyl-1,2-dithiol-1-ium salt similarly reacted with these reagents to afford the corresponding pyridines and pyridinone,[3] and consequently the behavior of **1** and the corresponding dithiolium salt toward these reagents was assumed to be the same.

Malononitrile, ethyl cyanoacetate, and diethylcarbamoylacetonitrile were heated to reflux with **1** in presence of sodium hydride, and then treated with hydrochloric acid to afford yellow powders of **5**, **6**, and **7** in 92, 42, and 47% yields respectively. Compounds **5** and **6** were confirmed to be 5-cyno- and 5-ethoxycarbonyl-4-mercapto-2,6-diphenylpyrimidine which are given by the reaction of 2,4,6-triphenyl-1,3,5-thiadiazin-1-ium salt with the two reagents.[5] The UV and IR spectra of **7** were similar to those of **5** and **6**. Its MS data and analytical results supported the conclusion that **7** is 5-diethylcarbamoyl-4-mercapto-2,6-diphenylpyrimidine.

On the other hand, benzoylacetonitrile and phenylsulfonylacetonitrile gave a common product, **8**, in 42 and 53% yields, respectively, when treated with **1** in the presence of sodium hydride. Its IR spectrum had an absorption assignable to a cyano group, but neither a benzoyl nor a phenylsulfonyl group. The molecular weight of **8** was determined by its MS data to be 262. These spectral data and the analytical results supported the assignment that **8** is 5-cyano-2,4-diphenylthiazole.

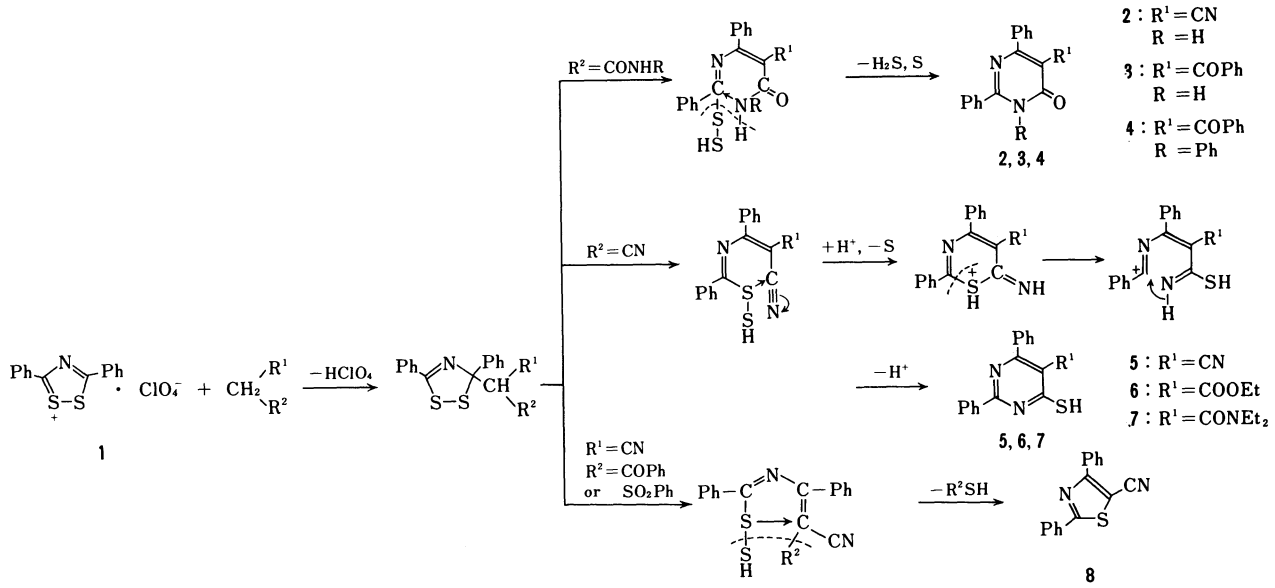
The reaction of the corresponding dithiolium salt with active methylene possessing ester groups gives a number of 2*H*-thiopyran-2-ones,[3] while the reaction of **1** with diethyl malonate and ethyl benzoylacetate did not give 6*H*-1,3-thiazin-6-ones. This fact suggested that **1** has no reaction mode in which an ester group of these reagents participates.

The results of forming **2**—**8** are summarized in Scheme 1.

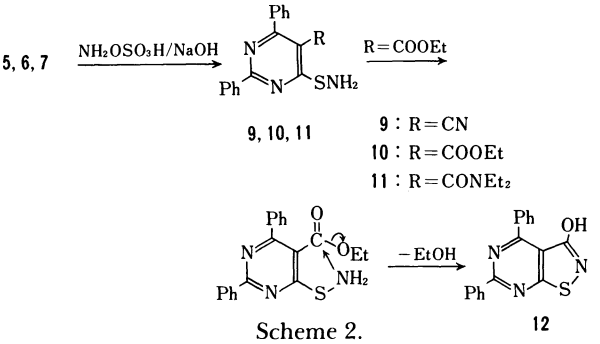
When treated with hydroxylamine-*O*-sulfonic acid in the presence of sodium hydroxide, **5** and **7** gave white powders of **9** and **11** in good yields. Their IR spectra have two absorptions assignable to the N–H stretching in the range of 3376—3244 cm^{-1} and an absorption of a pyrimidine ring at around 1525 cm^{-1}. Their molecular weights were determined by their MS data to be 304 and 378. These spectral data suggested that **9** and **11** are 4-(aminthio)-5-cyano- and 4-(aminothio)-5-diethylcarbamoyl-2,6-diphenylpyrimidines respectively. Their analytical results also supported the structure assignments. On treatment with hydroxyamine-*O*-sulfonic acid under the same conditions as the above, however, **6** did not give the corresponding aminothiopyrimidine, **10**, but another product, **12**, was obtained. The spectrum of **12** had no absorption assignable to an ester group (*ca.* 1750 cm^{-1}). The molecular weight was determined to be 305. The structure of **12** was thus confirmed by these spectral and the analytical data to be 3-hydroxy-4,6-diphenylisothiazolo[5,4-*d*]pyrimidine. The reaction could be assumed to proceed as follows: **6** leads to **10** in the same fashion as do the other two mercaptopyrimidines (**5** and **7**); however, **6** further cyclizes to form **12** together with the elimination of ethanol (Scheme 2). This process could be regarded as analogous to that forming 3-amino-4,6-dimethylisothiazolo[5,4-*b*]-pyridine.[6]

Experimental

Reactions of 1 with Cyanoacetamide, Benzoylacetamide, and Benzoylacetanilide. Into a solution of cyanoacetamide, benzoylacetamide, or benzoylacetanilide (1.5 mmol) in 1 mol dm^{-3} MeONa–MeOH (3 ml), **1** (0.36 g, 1.0 mmol) was added with stirring in small portions, and then heated to reflux for 1 h. The reaction mixture was poured into dilute hydrochloric acid. The resulting precipitate was filtered off and recrystallized from acetonitrile to afford 5-cyano- or 5-benzoyl-4-hydroxy-2,6-diphenylpyrimidine (**2**, **3**), or 5-benzoyl-2,3,6-triphenyl-4(3*H*)-pyrimidinone (**4**) in 92, 38, 44% yield. Their IR spectra could be completely superimposed on those of the authentic samples.[5]



Scheme 1.



Scheme 2.

Reaction of 1 with Malononitrile, Ethyl Cyanoacetate, and Diethylcarbamoylacetonitrile. Into a solution of malononitrile ethyl cyanoacetate, or diethylcarbamoylacetonitrile (1.5 mmol) and sodium hydride (0.10 g, 4.2 mmol) in THF (3 ml), **1** (0.36 g, 1.0 mmol) was added with stirring in small portions, and heated to reflux for 1 h. The reaction mixture was poured into dilute hydrochloric acid. The precipitate was separated by decantation, and dissolved again in 2 mol dm^{-3} HCl–EtOH (3 ml); the resulting mixture was allowed to stand overnight. The solution was poured into an excess amount of water. The resulting precipitate was recrystallized from acetonitrile (**5**, **6**) or ethanol (**7**) to give 5-cyano-, 5-ethoxycarbonyl-, or 5-diethylcarbamoyl-4-mercapto-2,6-diphenylpyrimidine (**5**, **6**, or **7**) in 92, 42, or 47% yield. The IR spectra and the melting points of **5** and **6** agreed with those of their authentic samples.[5] The data of 7 are presented below.

Mp, 266°C; IR (KBr), 3058—2872, 1609, 1552, 1496, and 1235 cm^{-1}. UV_{max} (EtOH), 256 (ε 25400), 314 (12600), and 381 nm (4100); MS *m/e*, (rel intensity) 364 (M^+, 11.5), 330 (M^+-SH, 20.5), 291 (M^+-NEt_2, 20.5), 264 (13.1), 104 (72.3), and 72 (Et_2N^+, 100). Found: C, 69.14; H, 5.80; N, 11.57; S, 8.53%. Calcd for $C_{21}H_{21}N_3SO$: C, 69.39; H, 5.82; N, 11.56; S, 8.82%.

5-Cyano-2,4-diphenylthiazole (8). Into a solution of benzoylacetonitrile (0.22 g, 1.5 mmol) and sodium hydride (0.10 g, 4.2 mmol) in THF (3 ml), **1** (0.36 g, 1.0 mmol) was added with stirring in small portions, heated to reflux for 1 h. The reaction mixture was poured into dilute hydrochloric acid, and the precipitate was recrystallized from cyclohexane to give 0.11 g (42%) or 0.14 g (53%) of **8**; m, 132°C. MS *m/e*, (rel intensity) 262 (M^+, 50.7), 159 (M^+-PhCN, 100), 115 (Ph_2N^+, 23.6). UV_{max} (EtOH), 266 (ε 31000) and 318 nm (12100). Found: C, 73.50; H, 3.67; N, 10.60; S, 12.56%. Calcd for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68; S, 12.72%.

4-(Aminothio)-5-cyano- and 4-(Aminothio)-5-diethylcarbamoyl-2,6-dipenylpyrimidine (9 and 11). Into a solution of hydroxylamine-*O*-sulfonic acid (0.50 g, 4.4 mmol) in 2 M NaOH (10 ml), **5** (0.29 g, 1.0 mmol) or **7** (0.37 g, 1.0 mmol) was added with stirring in small portions at 0—5°C, and then allowed to stand at room temperature overnight. The resulting white powders were filtered off and recrystallized from ethanol to give **9** (0.22 g, 72%) or **11** (0.24 g, 63%).

9: Mp, 147°C; IR (KBr), 3376, 3288, 2216, 1525, 1491, 1442, and 1379 cm^{-1}. UV_{max} (EtOH), 279 nm (ε 42800); MS *m/e*, (rel intensity) 304 (M^+, 75.1), 303 (M^+-1, 100), 153 (51.0), and 77 (39.7). Found: C, 67.23; H, 4.04; N, 18.16; S, 10.57%. Calcd for $C_{17}H_{12}N_4S$: C, 67.08; H, 3.98; N, 18.16; S, 10.57%.

11: Mp, 179°C; IR (KBr), 3344, 3244, 2984, 2940, 1621, 1525, 1496, 1446, and 1383 cm^{-1}. UV_{max} (EtOH), 262 nm (ε 36500). MS *m/e*, (rel intensity) 378 (M^+, 28.9), 306 (M^+-NEt_2, 82.5), 100 (Et_2NCO^+, 38.8). Found: C, 66.47; H, 5.86; N, 14.80; S, 8.47%. Calcd for $C_{21}H_{22}N_4SO$: C, 66.64; H, 5.86; N, 14.77; S, 8.67%.

3-Hydroxy-4,6-diphenylisothiazolo[5,4-d]pyrimidine (12). **6** was treated with hydroxylamine-*O*-sulfonic acid as the same conditions as described above. The reaction mixture was poured into dilute hydrochloric acid and the resulting precipitate was recrystallized from acetonitrile to give **12** (0.16 g, 53%). Mp, 297°C; IR (KBr), 3054, 2922, 2710, 1657, 1524, 1493, 1449, and 1395 cm^{-1}. UV_{max} (EtOH), 276 nm (ε 36500); MS *m/e*, (rel intensitey) 305 (M^+, 85.5), 272 (M^+-SH, 7.0), 202 (M^+-PhCN, 11.2), 159 (11.9), 152.5 ($M^+/2$, 14.1), 128 (PhC_3NH^+, 100). Found: C, 67.08; H, 3.52; N, 13.76; S, 10.50%. Calcd for $C_{17}H_{11}N_3SO$: C, 66.87; H, 3.63; N, 13.77; S, 10.28%.

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