Cyclic Condensations of 2-Amino-1,3,4-thiadiazole with 1,3-Dicarbonyl Compounds

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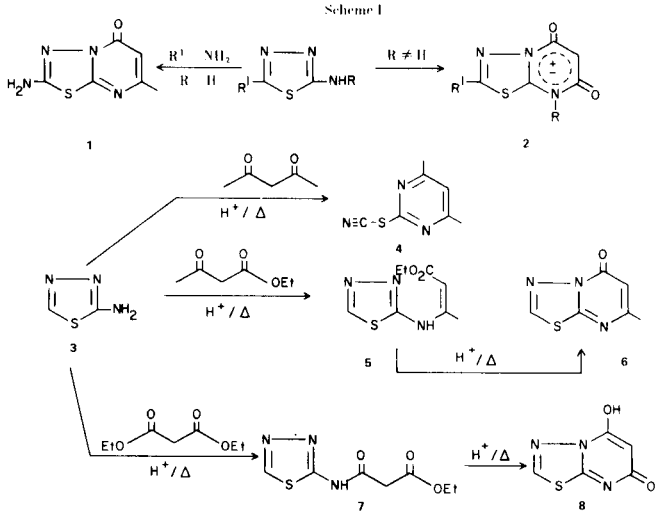
The reactions of 2-amino-1,3,4-thiadiazole with 1,3-dicarbonyl compounds are described. 2,4-Pentanedione gave 2-thiocyanato-4,6-dimethylpyrimidine while diethylmalonate and ethyl acetoacetate yielded 5-hydroxy-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one and 7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one, respectively. The structure of the latter compound was confirmed by a synthesis of the alternative isomeric structure (5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one) from 2-amino-1,3,4-thiadiazole and α-bromocrotonic acid.

J. Heterocyclic Chem., 13, 291 (1976).

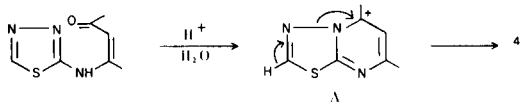
In the two reported instances of the condensation of 1,3-dicarbonyl compounds with substituted 2-amino-1,3,4-thiadiazoles (1,2) the expected fused bicyclic products **1** and **2** were obtained. While examining reactions of this type, we have discovered that in the case of the parent compound **3** two distinctively different products can be obtained depending on the type of 1,3-dicarbonyl compound employed.

Scheme I



When 2,4-pentanedione and 2-amino-1,3,4-thiadiazole (**3**) were condensed in toluene at reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid, a single product was produced in good yield. On the basis of spectroscopic and analytical data, the structure of this substance was ascertained to be that of 2-thiocyanato-4,6-dimethyl pyrimidine (**4**). With ethyl acetoacetate as the 1,3-dicarbonyl component, the same reaction conditions produced the bicyclic product **6**, plus some of its monocyclic precursor **5**, which could be converted into **6** by prolonged reflux in toluene. In the case of diethylmalonate as the 1,3-dicarbonyl component, it was necessary to use 1,2,4-trichlorobenzene at reflux as the reaction medium in order to obtain a characterizable product, since refluxing toluene gave no reaction. This was found to be the monocyclic compound **7**, which could be converted into the anticipated bicyclic product **8** by subsequent exposure to *p*-toluenesulfonic acid in refluxing toluene. On the basis of this limited data, it appears that the pathway leading to the thiocyanatopyrimidine is unique to the β-diketone type of 1,3-dicarbonyl component.

A possible explanation of this result involves the cation A as the immediate precursor of **4**. Only in the case of a β-diketone is the formation of such a cationic intermediate feasible.



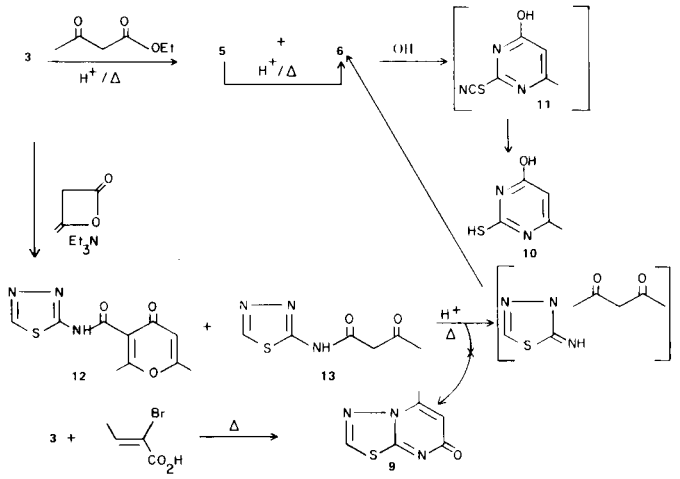
Product Structures.

2-Thiocyanato-4,6-dimethylpyrimidine (**4**) is a known compound (3). The melting point of material obtained in the present study agrees with the reported value and spectral data (ir 2165 cm^{-1}) are fully in accord with this structure.

A disparity between the melting point found for **6** (195-198°) and the value reported (158-160°) for this compound by Tsuji and Ueda (4) raised the question of whether or not the substance obtained in the present study

might in fact be the isomeric condensation product **9**. Moreover, in our hands mild basic hydrolysis of **6** produced the thiouracil **10** instead of the reported product **11** (5). These results prompted a synthesis of compound **9**.

Scheme II



The reaction of **3** with diketene in the presence of triethylamine produced equal amounts of **12** and **13**. The pyrone **12** was identified by comparison of its spectroscopic properties with a similar product obtained from 2-aminopyridine (6). 2-Acetoacetylamino-1,3,4-thiadiazole (**13**) is a known compound and its spectral properties and melting point agreed well with the literature values (4). Treatment of **13** with *p*-toluenesulfonic acid in refluxing toluene gave **6** as the only product. This rearrangement probably occurs by a [1,3] shift of the acetoacetyl group followed by cyclization, and is known to occur for the corresponding 2-pyridyl compounds (7,8).

A successful synthesis of **9** was accomplished by condensing **3** with α-bromocrotonic acid. The spectral properties of the product are in agreement with this structure and differ markedly from those of **6**. In addition, its melting point is 216-217.5°; thus it appears that the previously reported melting point for **6** (4) is in error.

The recent publication by Shafiee and Lalezari (9) on the reaction of 2-amino-1,3,4-selenadizaoles with acetylenic compounds, is in full agreement with our assignments for **6** and **9**.

The structures of compounds **7** and **8** are fully corroborated by their spectral properties.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus and are uncorrected. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Mass spectra were recorded on a CEC-110B instrument.

2-Amino-1,3,4-thiadiazole (**3**).

This compound was prepared by a modification of the literature procedures (10). A solution of 50 g. (0.54 mole) of thiosemicarbazide in 400 ml. of 88% formic acid was refluxed for 15 hours, evaporated *in vacuo* to dryness, then refluxed for 2 hours in 500 ml. of 10% hydrochloric acid. The resulting solution was then evaporated *in vacuo* to dryness again, the residue was dissolved in 350 ml. of hot water, made basic with 80 ml. of 50% sodium hydroxide, concentrated to 100 ml. and filtered. The solid was washed with water, dissolved in 800 ml. of hot methanol, treated with activated charcoal, filtered and concentrated to 150 ml. The product, 32 g., was collected and dried; concentration of the mother liquors gave a second crop, 3.1 g., for a total of 35.1 g. (65%), m.p. 196-197° (Lit. (10) 194-196°).

2-Thiocyanato-4,6-dimethylpyrimidine (**4**) (3).

A suspension of 10.1 g. (0.1 mole) of **3**, 30 ml. (0.29 mole) of 2,4-pentanedione and 100 mg. of *p*-toluenesulfonic acid monohydrate in 250 ml. of toluene was refluxed and stirred overnight with removal of water (3.5 ml.). The tarry suspension was cooled, filtered, evaporated *in vacuo* and the residue was chromatographed over 400 g. of silica gel using methylene chloride to give 8.5 g. (50%) of the title compound. An analytical sample was obtained from methylene chloride-petroleum ether as white prisms, m.p. 65-67° (Lit. (3) 65-67°); ir (chloroform): 2165 cm^{-1}; nmr (deuteriochloroform): 2.50 δ (s, 6H), 6.92 (s, 1H); uv: λ max 228 nm (ε = 12,193), 258 (3003); mass spectrum m/e 165 (M^+).

5-Hydroxy-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**8**).

A mixture of 60 g. (0.6 mole) of **3**, 160 ml. (1.05 moles) of diethyl malonate and 1.0 g. of *p*-toluenesulfonic acid monohydrate in 750 ml. of 1,2,4-trichlorobenzene was heated to 210° in an open flask. In 30 minutes a vigorous gas evolution occurred. The reaction was then cooled, filtered and the precipitate washed with ether followed by trituration with a large volume of boiling ethyl acetate. The hot slurry was filtered through silica gel, evaporated *in vacuo* and the residue treated with ether-petroleum ether to give 39.1 g. (30%) of ethyl [(1,3,4-thiadiazol-2-yl)-carbamoyl]acetate (**7**) as white prisms, m.p. 187-189° (methylene chloride-petroleum ether): ir (potassium bromide): 1721 and 1726 cm^{-1}; nmr (DMSO-d_6): 1.20 δ (t, J = 3 Hz, 3H), 3.65 (s, 2H), 4.15 (q, J = 3 Hz, 2H), 9.20 (s, 1H), 12.80 (broad s, 1H exchangeable with deuterium oxide); uv: λ max 250 nm (ε = 8,770).

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.1; H, 4.2; N, 19.5. Found: C, 38.9; H, 4.1; N, 19.8.

A suspension of 1.6 g. (7.4 mmoles) of **7** and 100 mg. of *p*-toluenesulfonic acid monohydrate in 120 ml. of toluene was refluxed overnight with removal of water. The reaction was cooled and the title compound collected, 800 mg. (64%), as pale yellow prisms, m.p. 230° dec. (methylene chloride-methanol): ir (potassium bromide): 2925 and 1620 cm^{-1}; nmr (DMSO-d_6): 5.28 δ (s, 1H) and 9.20 (s, 1H); uv: λ max 218 nm (ε = 27,462), 239 (12,844), infl. 275 (5,661); mass spectrum: m/e 169 (M^+).

Anal. Calcd. for $C_5H_3N_3O_2S$: C, 35.5; H, 1.8; N, 24.9. Found: C, 35.7; H, 2,0: N, 24.6.

7-Methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (4) (**6**) and Ethyl 3-[(1,3,4-Thiadiazol-2-yl)amino]-2-butenoate (**5**).

A suspension of 40 g. (0.4 mole) of **3**, 80 ml. (0.6 mole) of ethyl acetoacetate and 1.0 g. of *p*-toluenesulfonic acid monohy-

drate in 1 l. of toluene was refluxed for 48 hours with removal of water (9.5 ml.). The mixture was cooled, filtered and diluted with petroleum ether to give 20.5 g. of a white solid; the filtrate was saved and treated as in the next paragraph. Chromatography of the solid over 450 g. of silica gel using 5% ethanol-methylene chloride gave 12.5 g. (18.7%) of **6** as white needles, m.p. 195-198° (Lit. (4) 158-160°) (2-propanol); ir (chloroform): 1700 cm^{-1}; nmr (DMSO-d_6): 3.20 δ (s, 3H), 7.23 (s, 1H) and 9.70 (s, 1H); uv: λ max 212.5 nm (ε = 10,800), 217 (10,500), infl. 235 (4500), infl. 255 (3100) and 306 (8000); mass spectrum: m/e 167 (M^+).

Anal. Calcd. for $C_6H_5N_3OS$: C, 43.1; H, 3.0; N, 25.1; S, 19.2. Found: C, 43.2; H, 3.1; N, 25.3; S, 19.1.

Evaporation of the filtrate noted above and trituration with petroleum ether gave 39.4 g. of a solid which upon recrystallization from aqueous methanol, using activated charcoal, gave 13.6 g. (16%) of ethyl 3-[(1,3,4-thiadiazol-2-yl)amino]-2-butenoate (**5**) as white prisms, m.p. 106-108°; ir (chloroform): 1640 cm^{-1}; nmr (deuteriochloroform): 2.20 δ (t, J = 3 Hz, 3H), 3.35 (s, 3H), 5.00 (q, J = 3 Hz, 2H), 5.82 (s, 1H), 9.50 (s, 1H) and 11.64 (broad s, 1H, exchangeable with deuterium oxide; uv: λ max sh 250 nm (ε = 3,200) and 305.5 (25,150).

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.1; H, 5.2; N, 19.7. Found: C, 45.3; H, 5.2; N, 19.8.

6-Methyl-2-thiouracil (11) (**10**).

A solution of 500 mg. (3 mmoles) of **6** in 10 ml. of 1*N* aqueous sodium hydroxide was allowed to stand at room temperature for 1 hour. Acidification with acetic acid gave 300 mg. (71%) of **10** which upon recrystallization from methanol gave white prisms, m.p. 326-329° (Lit. (11) 325°); ir (potassium bromide): 3075 and 1610 cm^{-1}; nmr (DMSO-d_6): 2.05 δ (s, 3H), 5.68 (s, 1H) and 12.21 (broad s, 2H, exchangeable with deuterium oxide); uv: λ max 213.5 nm (ε = 16,330), 275.5 (14,910) and infl. 280 (14,626); mass spectrum: m/e 142 (M^+).

Anal. Calcd. for $C_5H_6N_2OS$: C, 42,3; H, 4.2; N, 19.7; S, 22.6. Found: C, 42,3; H, 4.2; N, 19.8; S, 22.4.

Cyclization of Ethyl 3-[(1,3,4-Thiadiazol-2-yl)amino]-2-butenoate (**5**).

A suspension of 2.0 g. (9 mmoles) of **5** and 100 mg. of *p*-toluenesulfonic acid monohydrate in 120 ml. of toluene was refluxed overnight with removal of water. Cooling gave the crude product which was chromatographed on 40 g. of silica gel using 10% ethanol-methylene chloride to give 800 mg. (54%) of **6**, m.p. 195-198° (2-propanol). All spectral data were superimposable with those of authentic material.

2-Acetoacetylamino-1,3,4-thiadiazole (**13**) (2) and 2,6-Dimethyl-3-[(1,3,4-thiadiazol-2-yl)carbamoyl]-4*H*-pyran-4-one (**12**).

A solution of 20 g. (0.2 mole) of **3**, 32.8 g. (0.4 mole) of diketene and 1 ml. of triethylamine in 500 ml. of toluene was refluxed overnight. Cooling gave a tan solid which was collected, washed with ether and recrystallized from methylene chloride-petroleum ether to give 14.7 g. of a solid which consisted of two components by tlc. Fractional crystallization from methylene chloride-petroleum ether gave 4.8 g. (13%) of the more polar product **13**, as white needles, m.p. 178-181°; (Lit. (2) 179-180°): ir (chloroform): 1710 and 1695 cm^{-1}; nmr (deuteriochloroform): indicated that 27% of the enol isomer was present; uv: λ max infl. 250.5 nm (ε = 8,200) and 277 (10,000).

Anal. Calcd. for $C_6H_7N_3O_2S$: C, 38.9; H, 3.8; N, 22.7. Found: C, 38.9; H, 3.8; N, 22.5.

Chromatography of the mother liquors, from above, over silica gel using 50% methylene chloride-ethyl acetate gave **12** as white prisms, m.p. 199-202° (methylene chloride-petroleum ether); ir (potassium bromide): 1660 and 1690 cm^{-1}; nmr (DMSO-d_6): 2.37 δ (s, 3H), 2.64 (s, 3H), 6.52 (s, 1H), 9.25 (s, 1H) and 13.60 (broad s, 1H, exchangeable with deuterium oxide); uv: λ max 208.5 nm (ε = 22,841), 246.5 (14,231) and sh 272 (10,542); mass spectrum: m/e 251 (M^+).

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.8; H, 3.6; N, 16.7; S, 12.8. Found: C, 47.8; H, 3.6; N, 16.8; S, 13.1.

Cyclization of 2-Acetoacetylamino-1,3,4-thiadiazole (**13**).

A suspension of 1.4 g. (7.5 mmoles) of **13** and 100 mg. of *p*-toluenesulfonic acid monohydrate in 120 ml. of toluene was refluxed overnight with removal of water. The mixture was cooled, filtered and evaporated *in vacuo*; trituration with ether gave 700 mg. of an off-white solid. Chromatography of the solid on 15 g. of silica gel using 10% methylene chloride-ethyl acetate gave 100 mg. (8%) of **6**, m.p. 195-198° (2-propanol). All spectral data were superimposable with those of authentic material.

5-Methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**9**).

A mixture of 9.0 g. (90 mmoles) of **3**, 13.6 g. (82.5 mmoles) of α-bromocrotonic acid (12) and 1.0 g. of *t*-butylcatechol was ground together and heated with stirring in an oil bath at 110°. In 23 minutes the internal reaction temperature reached 115°. [Note: The rate of heating is crucial. A too rapid rate causes a vigorous exothermic reaction from which no product could be isolated]. The mixture was then cooled and triturated with methanol to give 4.1 g. (27%) of the title compound as white prisms, m.p. 216-217.5° (aqueous ethanol); ir (potassium bromide): 1620 cm^{-1}; nmr (DMSO-d_6): 2.64 δ (s, 3H), 6.64 (s, 1H) and 9.60 (s, 1H); uv: λ max 212 nm (ε = 24,549) and 269 (12,057); mass spectrum: m/e 167 (M^+).

Anal. Calcd. for $C_6H_5N_3OS$: C, 43.1; H, 3.0; N, 25.1; S, 19.2. Found: C, 43.1; H, 2.9; N, 25.5; S, 19.2.

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