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Synthesis of 4-(*p*-Substituted Phenyl)-4,5-dihydro-5-oxo-1,3,4-thiadiazines

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4-(*p*-Substituted phenyl)-4,5-dihydro-5-oxo-thiadiazines were synthesized in fairly good yields by the reaction of phenylhydrazonomethylthioacetic acids with DCC in chloroform.

Keywords——*p*-substituted phenylhydrazonomethylthioacetic acid; methyl phenylhydrazonomethylthioacetate; 4-(*p*-substituted phenyl)-4,5-dihydro-5-oxo-1,3,4-thiadiazine; ring closure reaction

The synthesis and chemical properties of thiazole and thiadiazole analogs has been a subject of increasing interest in recent years because of their pharmacological and synthetic applications.[1-3] For this reason, and also in connection with our studies on the reactivities of pyridazinone and thioformimidate and their synthetic applications,[4,5] we wished to obtain 5-oxo-1,3,4-thiadiazines without a functional group at the 2-position. However, no report has appeared on the chemistry of 5-oxo-1,3,4-thiadiazine except for a paper on 4-phenyl-4,5-dihydro-5-oxo-thiadiazine.[6] Sato and Ohta described the synthesis of 4-phenyl-4,5-dihydro-5-oxo-1,3,4-thiadiazine (mp 181 °C) by the reaction of methyl phenylhydrazonomethylthioacetate **2** with sodium methoxide in methanol. Our recent work has revealed that the compound obtained by Sato *et al.* is not **1** but 2-phenylimino-1,3-thiazolidin-4-one **4**, and that **1** can be synthesized by the reaction of **2** with triethylamine in methanol. The structural investigation of **1** and **4** was carried out by proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy and X-ray analysis, and also by comparison with an authentic sample[7,8] (Chart 1). However, the reaction of **2** with triethylamine in methanol was found to give **1** in rather poor yield (44%), indicating that the formate **1** is in equilibrium with **2**. We now report the synthesis of **1a**—**d** from phenylhydrazonomethylthioacetic acids **3a**—**d** and dicyclohexylcarbodiimide (DCC) in chloroform (Chart 2). This ring closure reaction proceeds easily to give only the **1** derivatives in fairly good yields without side reactions. The results are summarized in Tables I and II.

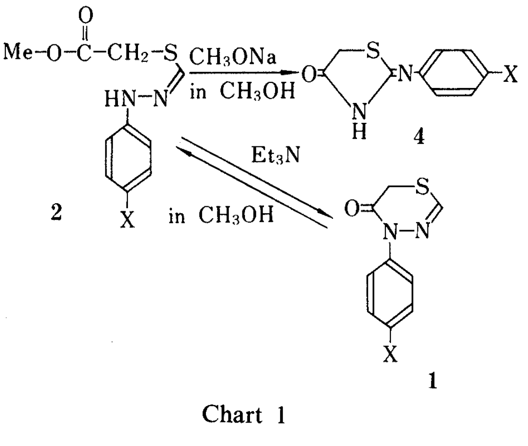

Chart 1

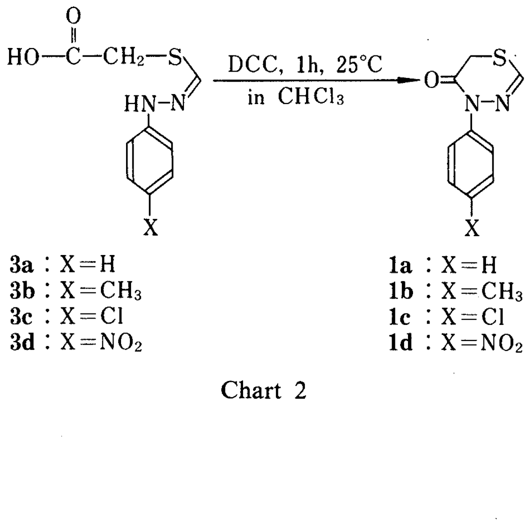

Chart 2

TABLE I. Synthesis of Phenylhydrazonomethylthioacetic Acids **3**

Product	Yield (%)	mp (°C)	Molecular formula[a]	IR (cm^{-1})		^{1}H-NMR (ppm)	
				$\nu C=O$	$\nu C=N$	δCH_2-	$\delta CH=$
3a	72	128—130 (130)[b]	$C_9H_{10}N_2O_2S$ (210)	1700	1590	3.80	7.22
3b	73	98—100	$C_{10}H_{12}N_2O_2S$ (224)	1710	1610	3.67	7.10
3c	46	103—105	$C_9H_9ClN_2O_2$ (244.5)	1720	1600	3.80	7.27
3d	78	167—170	$C_9H_9N_3O_4S$ (255)	1700	1590	3.86	7.50

a) All products gave satisfactory microanalyses: (C ±0.2, H ±0.25, N ±0.12).
b) Reported.[6]

TABLE II. Synthesis of 4-(*p*-Substituted Phenyl)-4,5-dihydro-5-oxo-1,3,4-thiadiazines **1**

Product	Yield (%)	mp (°C)	Molecular formula[a]	IR (cm^{-1}) $\nu C=O$	^{1}H-NMR (ppm)		
					$\delta CH=$	δPh	δCH_2-
1a	80	72—73	$C_9H_8N_2OS$ (192)	1640	7.73	7.40	3.53
1b	82	90—93	$C_{10}H_{10}N_2OS$ (206)	1660	7.73	7.24	3.54
1c	73	91—92	$C_9H_7ClN_2OS$ (226.5)	1660	7.76	7.38	3.56
1d	30	147—149	$C_9H_7N_3O_3S$ (237)	1660	7.86	7.76 —8.22	3.59

a) All products gave satisfactory microanalyses: (C ±0.2, H ±0.25, N ±0.12).

Experimental

Melting points were obtained on a Yanaco hot-stage apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-200 NMR spectrometer at 200 MHz with TMS as an internal standard. Infrared spectral data were collected on a JASCO IR-AL spectrometer with the samples in potassium bromide disks. High performance liquid chromatography (HPLC) was run on a Yanaco L-2000 high pressure liquid chromatograph using a pre-packed column of Yanaco GEL-5510 (4 mmϕ × 250 mm). Thin-layer chromatography and column chromatography were carried out using pre-coated Kieselgel 60-F254 sheets and Kieselgel 60 (240—400 mesh), respectively.

General Procedure for the Synthesis of 1 and 3——A typical experiment was performed as follows.

Phenylhydrazonomethylthioacetic Acid 3——A solution of sodium chloroacetate (11 mmol) in water (15 ml) was added dropwise to a mixture of the thioformylphenylhydrazine (10 mmol) and sodium hydroxide (10 mmol) in water (15 ml) and the mixture was stirred for 4 h at 25 °C. The reaction mixture was neutralized with 10% hydrochloric acid and the precipitate was collected and recrystallized from acetonitrile. The properties and yields of **3** are summarized in Table I.

4-(*p*-Substituted Phenyl)-4,5-dihydro-5-oxo-1,3,4-thiadiazines 1——A mixture of **3** (10 mmol) and dicyclohexylcarbodiimide (11 mmol) in chloroform (10 ml) was stirred for 1 h at room temperature. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was separated by column chromatography (ether–hexane) and recrystallized from hexane to give colorless needles of **1**. The properties and yields of the products **1** are summarized in Table II.

References and Notes

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8) The mechanism of the rearrangement from **1** to **4** will be reported in the near future.