

Synthesis and Hill Inhibitory Activity of New Substituted 3-Aryl-5-cyano-6-methylthio Pyrimidine-2,4-diones

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Novel substituted derivatives of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones were synthesized by the reaction of ethyl 2-cyano-3,3'-dimethylthioacrylate with arylureas in good yields. The structures of all title compounds were evaluated by elemental analyses and ^1H NMR spectra and compound **2c** was also confirmed by X-ray diffraction. Hill reaction inhibitory activity of title compounds was assayed.

Keywords Synthesis, Hill reaction inhibitory activity, 3-aryl-5-cyano-6-methylthio pyrimidine-2,4-dione

Introduction

Various heterocyclic compounds containing nitrogen atoms, especially uracils, have biologically interesting properties in medicinal and pesticidal chemistry as fungicides and herbicides.¹ The synthesis of uracils has been reported in the literature. It can be concluded that the key step is the substitution reaction of acrylates with substituted ureas.

In order to extend our recent studies^{2,3} on the application of ketoketene *N*,*S*-acetals in heterocyclic synthesis, we report the reaction of ethyl 2-cyano-3,3-bis(methylthio) acrylate (**1**) with substituted aromatic ureas, under mild condition, to give novel compounds 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones (**2**) (Scheme 1).

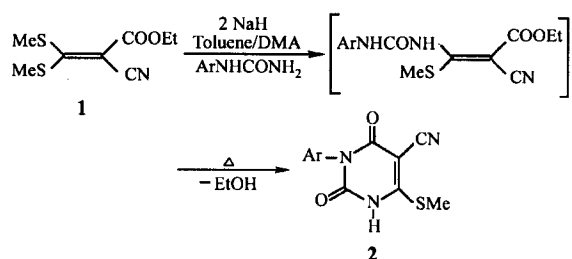
Experimental

Instruments

10–40 Mesh silica gel GF254 was used for the

TLC using a UV-detector. Melting points were determined with a Yanaco MT-500 apparatus without correction. ^1H NMR spectra were obtained with a Bruker AC-P200 spectrometer using TMS as the internal standard. Elementary analyses were obtained using a CHN Corder MT-3 elemental analyzer.

Scheme 1



General procedure for the synthesis of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones (**2a–n**)

To a solution of anhydrous toluene (50 mL) and anhydrous *N,N*-dimethylacetamide (50 mL), 20 mmol of sodium hydride, 10 mmol of ethyl 2-cyano-3,3-dimethylthioacrylate and 10 mmol of aryl urea were added in a proper order. The reaction mixture was stirred at room temperature until the reaction was complete as monitored by TLC (eluent acetone : petroleum ether = 2:1). Then the mixture was poured into 50 mL of ice water and the water layer was acidified with 10% hydrochloric acid. The resulting precipitate was collected

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by filtration under pressure, and refluxed in 20 mL of anhydrous ethanol for 4 h. The resulting precipitate was collected by filtration under pressure, and recrystallized from acetone/petroleum ether. Thus, 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones **2a**—**n** were obtained.

All these compounds were characterized by elemen-

tal analyses and ^1H NMR spectroscopy (Tables 1 and 2) and some compounds were further confirmed by IR and MS. For example, the data of IR and MS of compound **2a** are listed as follows: IR (KBr) ν : 3223, 2996, 2211, 1734, 1663, 1593, 1532, 1411 cm^{-1} ; MS m/z (%): 259 (M^+ , 39), 119 (100), 64 (6).

Table 1 Physical constants and elemental analyses of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones

Comp.	Ar	Formula	Yield (%)	m. p. ($^{\circ}\text{C}$)	Analysis [Calcd./Found]		
					C	H	N
2a	C_6H_5	$\text{C}_{12}\text{H}_9\text{N}_3\text{O}_2\text{S}$	84	> 300	55.60 (55.78)	3.47 (3.38)	16.22 (16.01)
2b	<i>p</i> - ClC_6H_4	$\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}_2\text{S}$	86	> 300	49.06 (49.28)	2.72 (2.93)	14.31 (14.50)
2c	<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4$	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$	91	> 300	53.98 (53.95)	4.49 (4.00)	14.53 (14.30)
2d	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$	88	> 300	57.14 (57.35)	4.03 (4.00)	15.38 (15.40)
2e	<i>o</i> - $\text{CH}_3\text{OC}_6\text{H}_4$	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$	84	> 300	53.98 (53.99)	3.81 (3.71)	14.53 (14.30)
2f	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$	86	251—253	57.14 (57.42)	4.03 (4.15)	15.38 (15.56)
2g	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$	84	265—266.5	57.14 (57.42)	4.03 (4.28)	15.38 (15.43)
2h	2,4-(CH_3) $_2\text{C}_6\text{H}_3$	$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$	90	> 300	58.54 (58.54)	4.53 (4.10)	14.63 (14.82)
2i	<i>o</i> - ClC_6H_4	$\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}_2\text{S}$	86	> 300	49.06 (48.86)	2.73 (2.85)	14.30 (14.52)
2j	2,5-(CH_3) $_2\text{C}_6\text{H}_3$	$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$	89	> 300	58.54 (58.46)	4.53 (4.31)	14.63 (14.54)
2k	<i>m</i> - ClC_6H_4	$\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}_2\text{S}$	87	> 300	49.06 (49.90)	2.73 (3.77)	14.30 (14.48)
2l	3,4- $\text{Cl}_2\text{C}_6\text{H}_3$	$\text{C}_{12}\text{H}_7\text{Cl}_2\text{N}_3\text{O}_2\text{S}$	81	> 300	43.90 (44.01)	2.13 (2.57)	12.80 (12.56)
2m	2,4- $\text{Cl}_2\text{C}_6\text{H}_3$	$\text{C}_{12}\text{H}_7\text{Cl}_2\text{N}_3\text{O}_2\text{S}$	88	> 300	43.90 (43.89)	2.13 (2.33)	12.80 (12.67)
2n	4- FC_6H_4	$\text{C}_{12}\text{H}_8\text{FN}_3\text{O}_2\text{S}$	85	> 300	51.99 (51.92)	2.89 (2.90)	15.16 (15.32)

X-ray diffraction experiment

The compound (Ar = *p*- $\text{CH}_3\text{OC}_6\text{H}_4$, **2c**) was recrystallized in acetone/petroleum ether. A light yellow crystal of **2c** having approximate dimensions of $0.40 \times 0.30 \times 0.60$ mm was mounted on a glass fiber in a random orientation and the crystal structure determined by X-ray diffraction. Preliminary examination and data collection were performed with Mo K_α radiation ($\lambda =$

0.071073 nm) on an Entrf-Nonius CAD4 diffractometer equipped with a graphite crystal, incident beam monochromator. The crystal belongs to the monoclinic system, space group $P2_1/n$ with parameters: $a = 1.1602(2)$, $b = 1.5921(3)$, $c = 1.3918(3)$ nm, $\beta = 94.38(3)^\circ$, $V = 2.563(1)$ nm^3 , $z = 4$, $D_x = 1.499$ g/cm^3 , $\mu = 0.264$ mm^{-1} , $S = 0.84$, $F(000) = 1200$. A total of 2959 independent reflections were collected in the range of $2 \leq \theta \leq 29.3^\circ$ by $\omega - 2\theta$ scan technique at

room temperature, in which 1692 reflections with $I \geq 3\sigma$ (I) were considered to be observed and used in the suc-

cessive refinements. The correction for L_p factors was applied to the data.

Table 2 ^1H NMR data of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones

Compound	^1H NMR (δ , DMSO)
2a	2.76 (s, 3H, CH ₃ S), 7.24–7.47 (m, 5H, C ₆ H ₅), 8.19 (w, 1H, NH)
2b	2.78 (s, 3H, CH ₃ S), 7.22–7.56 (m, 4H, C ₆ H ₄), 8.20 (w, 1H, NH)
2c	2.80 (s, 3H, CH ₃ S), 3.84 (s, 3H, CH ₃ O), 6.96–7.24 (m, 4H, C ₆ H ₄), 8.16 (w, 1H, NH)
2d	2.38 (s, 3H, CH ₃), 2.54 (s, 3H, CH ₃ S), 7.03–7.28 (m, 4H, C ₆ H ₄), 10.12 (w, 1H, NH)
2e	2.42 (s, 3H, CH ₃ S), 3.78 (s, 3H, CH ₃ O), 6.98–7.24 (m, 4H, C ₆ H ₄), 9.98 (w, 1H, NH)
2f	2.13 (s, 3H, CH ₃), 2.47 (s, 3H, CH ₃ S), 6.98–7.26 (m, 4H, C ₆ H ₄), 9.62 (w, 1H, NH)
2g	2.37 (s, 3H, CH ₃), 2.56 (s, 3H, CH ₃ S), 6.94–7.22 (m, 4H, C ₆ H ₄), 9.24 (w, 1H, NH)
2h	2.08 (s, 3H, CH ₃), 2.31 (s, 3H, CH ₃), 2.50 (s, 3H, CH ₃ S), 6.87–7.23 (m, 3H, C ₆ H ₃), 9.24 (w, 1H, NH)
2i	2.76 (s, 3H, CH ₃ S), 7.24–7.51 (m, 4H, C ₆ H ₄), 8.27 (w, 1H, NH)
2j	2.09 (s, 3H, CH ₃), 2.34 (s, 3H, CH ₃), 2.57 (s, 3H, CH ₃ S), 6.94–7.24 (m, 3H, C ₆ H ₃), 9.28 (w, 1H, NH)
2k	2.77 (s, 3H, CH ₃ S), 7.22–7.50 (m, 4H, C ₆ H ₄), 8.22 (w, 1H, NH)
2l	2.78 (s, 3H, CH ₃ S), 7.20–7.49 (m, 3H, C ₆ H ₃), 8.20 (w, 1H, NH)
2m	2.78 (s, 3H, CH ₃ S), 7.21–7.52 (m, 3H, C ₆ H ₃), 8.21 (w, 1H, NH)
2n	2.77 (s, 3H, CH ₃ S), 7.24–7.51 (m, 4H, C ₆ H ₄), 8.23 (w, 1H, NH)

The structure was solved by direct methods (MULTAN 82). Most of the non-hydrogen atoms were located from an E-map. The coordinates of remaining non-hydrogen atoms and part of hydrogen atoms were found in the successive difference Fourier syntheses. The final refinement by full matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms was converged with unweighted and weighted agreement factors of 0.054 and 0.059 ($\omega = 1$).

The highest peak on the final difference Fourier map and the final least-squares cycle were 280 and -330 e/nm^3 , respectively ($(\Delta/\sigma)_{\text{max}} = 0.001$). All calculations were performed on a PDP 11/44 and IBM 486 computer using SDP-PLUS program system.

Results and discussion

Aromatic ureas are with generally low reactivity due to their reduced nucleophilicity. It was found that in the presence of sodium hydride, and under the mild condition, compounds **1** could easily react with aromatic ureas, and thus gave the intermediate ethyl 2-cyano-3-methylthio-3'-substituted urea-acrylate, which was refluxed in anhydrous alcohol to give the title compounds 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones **2**. It was also found that a mixture of *N,N*-dimethylac-

etamide (DMA)/toluene was particularly suitable for the substitution reaction. The physical properties and ^1H NMR spectra of the products are listed in Tables 1 and 2, respectively. However, these data are insufficient to confirm whether there is a uracil-ring formed or not. This prompted us to carry out an X-ray diffraction analysis of one of the products. It was found from X-ray diffraction that two molecules of this compound are associated *via* hydrogen-bond interaction between the amino hydrogen and carbonyl oxygen atoms (Fig. 1).

Hill reaction inhibitory activity

Compounds were assayed for Hill reaction inhibitory activity using suspensions of chloroplasts isolated from the leaves of 20 day-old plants of *Pisum sativum*. The experimental procedure was described elsewhere.⁴ The activity of a compound as a Hill inhibitor was expressed in terms of its pI_{50} value *i. e.* $-\lg IC_{50}$, where IC_{50} was the molar concentration required to decrease the rate of dye reduction under illumination of saturating intensity to 50% obtained in the absence of the compound. The Hill-reaction inhibitory activities of compounds **2a–n** were recorded in Table 3. Results from bioassay test indicate that some of the designed and synthesized title compounds have good activity, especially, compound **2i** showed high activity.

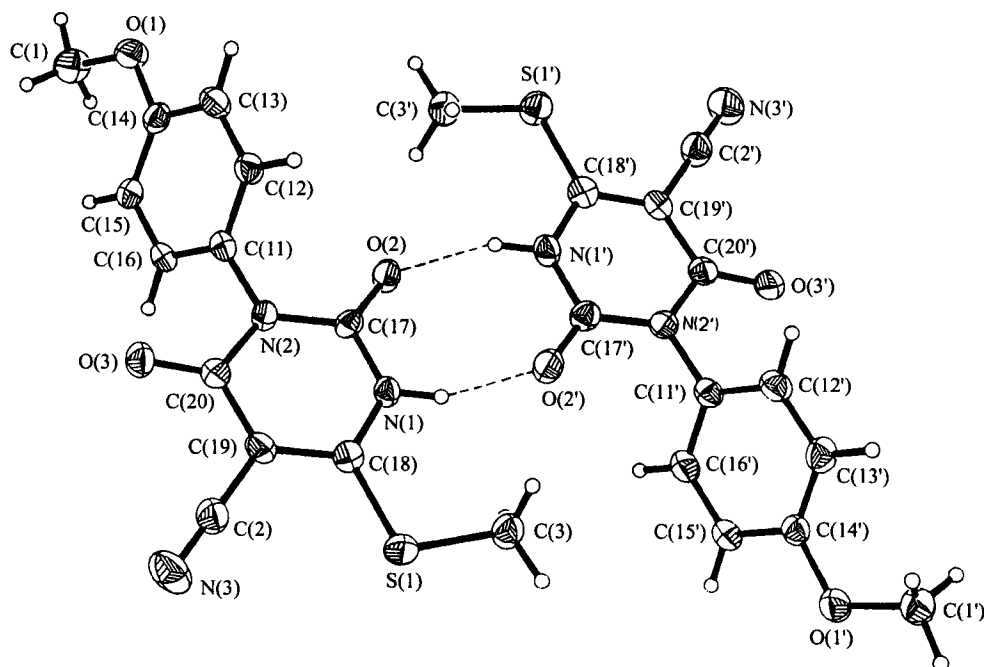


Fig. 1 Crystal structure of compound 2c.

Table 3 Hill reaction inhibitory activity of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones

Compound	Ar	pl_{50}	Compound	Ar	pl_{50}
2a	C ₆ H ₅	5.55	2h	2,4-(CH ₃) ₂ C ₆ H ₃	3.94
2b	<i>p</i> -ClC ₆ H ₄	5.84	2i	<i>o</i> -ClC ₆ H ₄	6.37
2c	<i>p</i> -CH ₃ OC ₆ H ₄	5.57	2j	2,5-(CH ₃) ₂ C ₆ H ₃	3.27
2d	<i>p</i> -CH ₃ C ₆ H ₄	4.30	2k	<i>m</i> -ClC ₆ H ₄	5.90
2e	<i>o</i> -CH ₃ OC ₆ H ₄	4.25	2l	3,4-Cl ₂ C ₆ H ₃	4.93
2f	<i>o</i> -CH ₃ C ₆ H ₄	4.56	2m	2,4-Cl ₂ C ₆ H ₃	4.14
2g	<i>m</i> -CH ₃ C ₆ H ₄	5.19	2n	4-FC ₆ H ₄	4.72

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