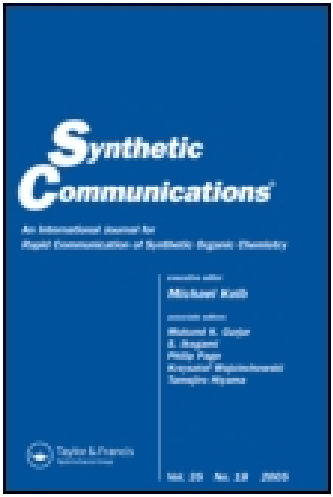

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A Facile Synthesis of 3-Aryl-5-cyano-6-methylthio-pyrimidine-2,4-diones

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A FACILE SYNTHESIS OF 3-ARYL-5-CYANO-6-METHYLTHIO-PYRIMIDINE-2, 4-DIONES

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ABSTRACT: Novel derivatives of 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones were synthesized, under mild conditions, by the reaction of ethyl 2-cyano-3,3'dimethylthioacrylate with arylureas.

Polarized ketene dithioacetals 1, $(XY)C{=}C(SR)_2$ (X, Y=CN, NO_2, COOEt, $CONH_2$; R=alkyl, benzyl), have been extensively used as building blocks in organic synthesis especially in the preparation of heterocyclic compounds[1, 2]. Compound **1a** can react as a Michael acceptor with various nucleophiles such as hydrazine, hydroxyamines, amines, Grignard reagents to give corresponding α-substituted products by an addition-elimination reaction.

Various heterocyclic compounds containing nitrogen atoms, especially uracils, have biologically interesting properties in medicinal and pesticidal chemistry for example as fungicides, herbicides[3]. 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 an extension of our recent studies[4, 5] in the application of ketoketene N, S-acetals in heterocyclic synthesis, we report herein the reaction ethyl 2-cyano-3,3-bis(methylthio)acrylate (**1a**) with substituted aromatic ureas, under mild conditions, to give the novel title compounds 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-diones

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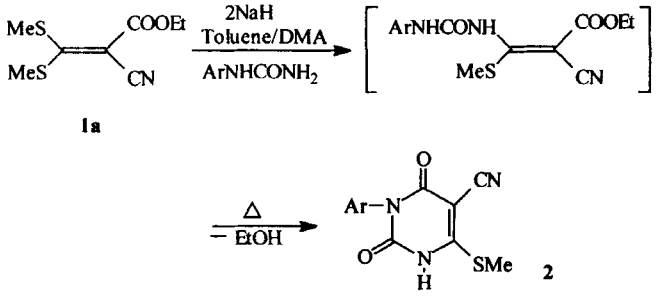

Aromatic ureas are generally reactive to give only low yields due to their reduced nucleophilicity. It was found that in the presence of sodium hydride, and under mild conditions, compound **1a** reacted readily with aromatic ureas, and thus gave the intermediate ethyl 2-cyano-3-methylthio-3'-substitutedurea-acrylates, which when refluxed in anhydrous alcohol gave the title uracils. It was also found that a mixture of N, N-dimethylacetamide (DMA) /toluene are particularly suitable for the substitution reaction.

The compound (Ar = *p*-$CH_3OC_6H_4$, **2c**) was recrystallized in acetone/petroleum, and the crystal structure was determined by X-ray. It was found that two molecules of this compound are associated via H-bond interaction between the amino hydrogen and carbonyl oxygen atoms.

EXPERIMENTAL

10~40 Silica gel GF254 was used for the TLC and detection was carried out on a UV-detector. Melting points were determined with a Yanaco MT-500 apparatus without correction. ^{1}H NMR spectra are obtained with Brucker AC-p200 spectrometer using TMS as an internal standard. Elementary analyses were obtained using a CHN Corder MT-3 elemental analyzer.

Synthesis of 3-phenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2a**)

To a solution of 50ml anhydrous toluene and 50ml anhydrous N, N-dimethylacetamide, 0.96g(50%, 20mmol) sodium hydride, 2.17g(10mmol) ethyl 2-cyano-3,3-dimethylthioacrylate and 1.36g(10mmol) phenyl urea was added in proper order. The reaction mixture was stirred at room temperature until the reaction was complete monitored

by TLC (acetone: petroleum 2:1). Then the mixture was poured into 50ml of ice-water, the water layer was acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration under pressure, and was refluxed in 20ml anhydrous alcohol for 4hours. The resulting precipitate was collected by filtration under pressure to give 2.18g(8.4mmol) of colorless needless, m.p. >300 ℃, yield 84%. ^1H NMR(DMSO-d6, ppm): 2.76(s, 3H, CH_3S), 7.24~7.47(m, 5H, C_6H_5), 8.19(ω, 1H, NH)); Anal. Calcd. For $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.47; N, 16.22. Found: C, 55.78; H, 3.38; N, 16.01.

Synthesis of 3-*p*'-chlorophenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2b**)

This compound was synthesized in 86% yield from **1** (2.17g, 10mmol) and *p*-chlorophenyl urea (1.71g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^1H NMR(DMSO-d6, ppm): 2.78(s, 3H, CH_3S), 7.22~7.56(m, 4H, C_6H_4), 8.20(ω, 1H, NH); Anal. Calcd. For $C_{12}H_8N_3O_2ClS$: C, 49.06; H, 2.72; N, 14.31. Found: C, 49.28; H, 2.93; N, 14.50.

Synthesis of 3-*p*'-methoxylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2c**)

This compound was synthesized in 91% yield from **1** (2.17g, 10mmol) and *p*-methoxylphenyl urea (1.66g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^1H NMR(DMSO-d6, ppm): 2.80(s, 3H, CH_3S), 3.84(s, 3H, CH_3O), 6.96~7.24(m, 4H, C_6H_4), 8.16(ω, 1H, NH); Anal. Calcd. For $C_{13}H_{11}N_3O_3S$: C, 53.98; H, 3.81; N, 14.53. Found: C, 53.95; H, 4.00; N, 14.30.

3-*p*'-Methoxylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2c**) was recrystallized in acetone/petroleum in space group $P2_{1/n}$ with a=1.1602(2)nm, b= 1.5921(3)nm, c=1.3918(3)nm, β=94.38(3)° for Z=8, R=0.054.

Synthesis of 3-*p*'-methylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2d**)

This compound was synthesized in 88% yield from **1** (2.17g, 10mmol) and *p*-methylphenyl urea (1.50g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^1H NMR(DMSO-d6, ppm): 2.38(s, 3H, CH_3), 2.54(s, 3H, CH_3S), 7.03~7.28(m, 4H, C_6H_4), 10.12(ω, 1H, NH); Anal. Calcd. For $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.03; N, 15.38. Found: C, 57.35; H, 4.00; N, 15.40.

Synthesis of 3-*o*'-methoxylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2e**)

This compound was synthesized in 84% yield from **1** (2.17g, 10mmol) and *o*-

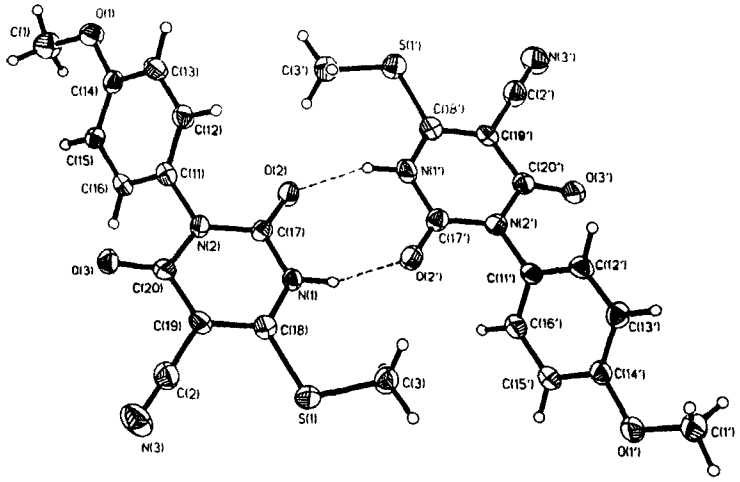

Figure 1 Crystal structure of title compound(Ar = *p*-$CH_3OC_6H_4$, 2c)

methoxylphenyl urea (1.66g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.42(s, 3H, CH_3S), 3.78(s, 3H, CH_3O), 6.98~7.24(m, 4H, C_6H_4), 9.98(ω, 1H, NH); Anal. Calcd. For $C_{13}H_{11}N_3O_3S$: C, 53.98; H, 3.81; N, 14.53. Found: C, 53.99; H, 3.71; N, 14.30.

Synthesis of 3-*o*'-methylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2f**)

This compound was synthesized in 86% yield from **1** (2.17g, 10mmol) and *o*-methylphenyl urea (1.50g, 10mmol) in a manner similar to that describe for **2a**. m. p. 251~253 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.13(s, 3H, CH_3), 2.47(s, 3H, CH_3S), 6.98~7.26(m, 4H, C_6H_4), 9.62(ω, 1H, NH); Anal. Calcd. For $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.03; N, 15.38. Found: C, 57.42; H, 4.15; N, 15.56.

Synthesis of 3-*m*'-methylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2g**)

This compound was synthesized in 84% yield from **1** (2.17g, 10mmol) and *m*-methylphenyl urea (1.50g, 10mmol) in a manner similar to that describe for **2a**. m. p. 265~266.5 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.37(s, 3H, CH_3), 2.56(s, 3H, CH_3S), 6.94~7.22(m, 4H, C_6H_4), 9.24(ω, 1H, NH); Anal. Calcd. For $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.03; N, 15.38. Found: C, 57.42; H, 4.28; N, 15.43.

Synthesis of 3-*2',4'*-dimethylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2h**)

This compound was synthesized in 90% yield from **1** (2.17g, 10mmol) and *2,4*-dimethylphenyl urea (1.64g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.08(s, 3H, CH_3), 2.31(s, 3H, CH_3), 2.50(s, 3H, CH_3S), 6.87~7.23(m, 3H, C_6H_3), 9.24(ω, 1H, NH); Anal. Calcd. For $C_{14}H_{13}N_3O_2S$: C, 58.54; H, 4.53; N, 14.63. Found: C, 58.54; H, 4.10; N, 14.82.

Synthesis of 3-*o'*-chlorophenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2i**)

This compound was synthesized in 86% yield from **1** (2.17g, 10mmol) and *o*-chlorophenyl urea (1.71g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.76(s, 3H, CH_3S), 7.44~7.51(m, 4H, C_6H_4), 8.27(ω, 1H, NH); Anal. Calcd. For $C_{12}H_8N_3O_2ClS$: C, 49.06; H, 2.72; N, 14.31. Found: C, 48.86; H, 2.85; N, 14.52.

Synthesis of 3-*2',5'*-dimethylphenyl-5-cyano-6-methylthiopyrimidine-2,4-diones(**2j**)

This compound was synthesized in 89% yield from **1** (2.17g, 10mmol) and *2,5*-dimethylphenyl urea (1.64g, 10mmol) in a manner similar to that describe for **2a**. m. p. >300 ℃. ^{1}H NMR(DMSO-d6, ppm): 2.09(s, 3H, CH_3), 2.34(s, 3H, CH_3), 2.57(s, 3H, CH_3S), 6.94~7.24(m, 3H, C_6H_3), 9.28(ω, 1H, NH); Anal. Calcd. For $C_{14}H_{13}N_3O_2S$: C, 58.54; H, 4.53; N, 14.63. Found: C, 58.46; H, 4.31; N, 14.54.

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