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Note

Chromium(III) chloride catalyzed one-pot synthesis of pyrimidine-2-thiones from arylidines and thioureas

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An efficient and high yielding method for two component, one-pot synthesis of pyrimidine-2-thiones from arylidines and thioureas using chromium(III) chloride as catalyst under aqueous conditions is reported.

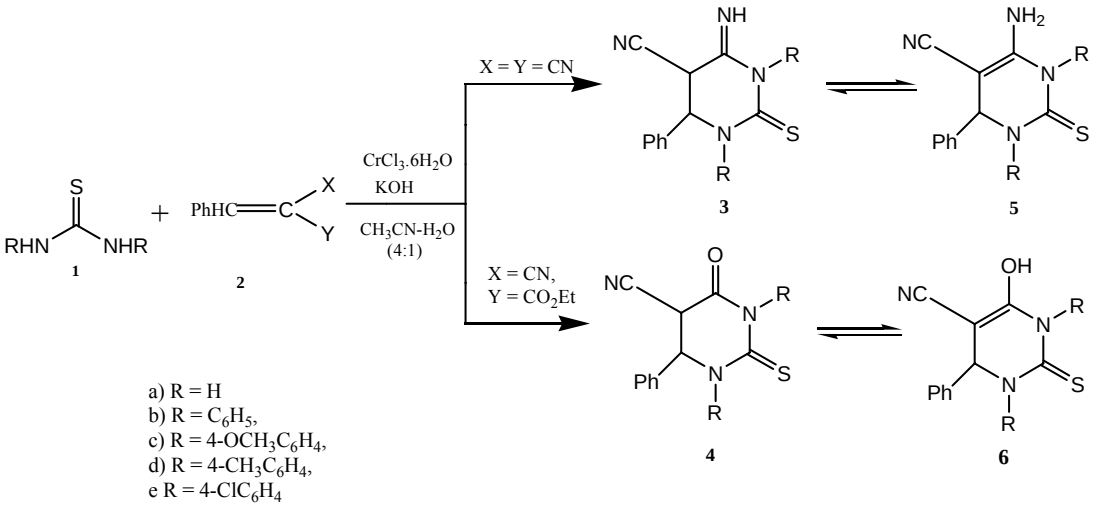
Keywords: Chromium chloride, synthesis, pyrimidine-2-thiones, arylidines, thioureas

The application of pyrimidine-2-thiones, such as 2-thiouracils and 2-thiocytosines, to the treatment of hyperthyroidism in man suggested a study of the preparation and properties of a series of substituted pyrimidine-2-thiones. A number of the alkyl pyrimidine-2-thiones, particularly those substituted in the 6-position, showed considerably greater anti-thyroid activity in rats than pyrimidine-2-thiones itself[1]. Pyrimidine-2-thiones and their derivatives are also known to exhibit biological activities[2], such as antiviral, antitumor, antibacterial, anti-inflammatory, antihypertension, etc. The condensation of thiourea and ethyl ethoxymethylene cyanoacetate was reported by Ulbricht and Price[3] to yield two products. 5-Carbethoxy-2-thiocytosine was obtained as the major product and 5-cyano-2-thiouracil as a minor component. However, when ethyl phenylmethylene cyanoacetate was allowed to react with thioureas, the products were not 5-carbethoxy-2-thiocytosines but were 2-thiouracils. The reactions of thioureas with ethoxymethylene derivatives of diethyl malonate, ethyl cyanoacetate and ethyl oxalacetate to yield 5-cyano-, 5-keto- and 5-carbethoxy-2-thiouracils and thiocytosines were also reported[4].

Biginelli's reaction for the synthesis of pyrimidine-2-thiones and their derivatives involved three component, one-pot condensation of a β-ketoesters with an aldehyde and thioureas under strongly acidic conditions[2,5] and several improved procedures have recently been reported[6]. However, most of these reactions required expensive reagents, strongly acidic conditions, high temperatures and moreover, these methods involved three component. In continuation of our interest in the synthesis of fused pyrimidines[7], herein we report an efficient and high yielding method for two component, one-pot synthesis of pyrimidine-2-thiones using chromium(III) chloride as catalyst under aqueous conditions, which not only is very simple and high yielding (83-98%) but also greatly decreases environmental concerns (**Scheme I**).

We have tested a variety of reaction conditions with the model reaction using chromium (III) chloride as a catalyst in acetonitrile-water (4:1) medium. It seems that acetonitrile-water is a much better solvent (> 93%) than all other tested solvents such as ethanol (~ 65%), water (72%), and THF (45%). The yields can be improved by allowing the reaction at refluxing condition in presence of KOH and ethanol without any catalyst. But the best results were obtained by carrying out the reaction at room temperature in the presence of catalytic amount of chromium (III) chloride in presence of CH_3CN-H_2O (4:1). Reactions in aqueous media are especially appealing, as they provide an opportunity to work with an open vessel, thus avoiding the risk of high internal pressure development. Under these conditions, the yields are significantly raised (88-98 %), the crude products obtained are of high purity (> 95 %) by ^{1}H NMR and moreover, can avoid using harmful organic solvents.

Ethyl phenylmethylenemalononitrile reacted with N-arylthioureas to give excellent yields of 4-amino-5-cyano-6-phenyl-pyrimidine-2-thiones **5**, which are derived from the intermediates 6-phenyl-2-thio-cytosines **3**. However, when ethyl phenylmethylene-cyanoacetate was allowed to react with the above thioureas, the products were not 5-carbethoxy-6-phenyl-2-thiocytosines but an equally good yield of 4-hydroxy-5-cyano-6-phenyl-pyrimidine-2-thiones **6**, which are derived from 6-phenyl-2-thiouracils **4**, were obtained. This striking and complete change in the course of the cyclization was obviously due to the presence of phenyl on the β-carbon of arylidine **2**. A possible reason is seen for the formation of thiouracils rather than thiocytosines, when the intermediates in



Scheme I

these reactions are considered. Intermediates in reactions of this type were shown to be ureidomethylenecyanoacetates for which two structures **A** and **B** may be written. It is suggested by reason of steric factors that structure **A** is more stable thermodynamically than **B**, as the phenyl group is larger than the NH group, and the CO_2Et group is in turn larger than the linear CN group. Structure **A** with these larger groups in an *anti* position is therefore more stable than a structure would be with these groups in a *syn* position. It is apparent from Stuart-Briegleb molecular models that structure **A** can cyclize only one way and that is to yield the 6-phenyl-2-thiouracils **4**, not 5-carbethoxy-6-phenyl-2-thiocytosines. This argument does not preclude the possibility that configurations **A** and **B** may be predetermined by *syn* or *anti* forms of the arylidines.

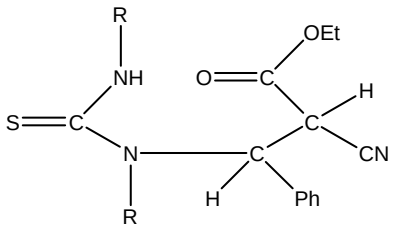
In conclusion, we have developed a simple, efficient and general method for the synthesis of pyrimidine-2-thiones using the inexpensive, less toxic and commercially available catalyst. Moreover, the present method offered several advantages including high yields, simple work-up procedures and eco-friendly reactions.

Experimental Section

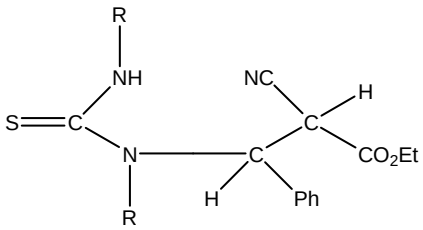
General Procedure. Melting points were determined by capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. All samples were run as a thin film (produced by evaporation of a chloroform solution) on a sodium chloride plate. Absorption maxima were recorded in wave numbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian unity 500 (500 MHz), Bruker AC-300 and Varian XL (300 MHZ) spectrometers. ^{13}Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AC-300 and Varian XL (75 MHz) spectrometers. Residual non-deuterated solvent was used as an internal reference and all chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) downfield from tetramethyl silane (TMS). All samples were run in deutero-chloroform ($CDCl_3$) as solvent unless otherwise stated. Mass spectra were recorded on a Kratas concept-IS mass spectrometer couples to a Mach 3 data system, or on a Jeol-D 300 mass spectrometer.

Typical procedure for the synthesis of thiocytosines. A solution of ethyl phenylmethylenemalononitrile (308 mg, 2 mmoles) and N,N-diphenylthiourea (2.5 mmole) in acetonitrile (20 mL)-water (5 mL) was stirred at room temperature in the presence of KOH (0.5 g) and chromium(III) chloride (20 mol%) for 24 hr (TLC). The reaction mixture was poured onto crushed ice (20 g) and the solid product separated was filtered under suction, washed with cold water (20 mL) and then recrystallized from ethanol to afford 5-cyano-6-phenyl-2-thiocytosine **3a**; m.p. 190-192ºC; IR (KBr): 3479, 3339, 3223, 2220, 1634, 1531, 1298, 1242, 1160, 768 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 9.34 (1H, br, s, NH), 8.73 (1H, br s, NH), 8.05 (1H, d, J = 8.6 Hz, 5-H), 7.49-7.63 (3H, m, Ar), 7.35- 7.42(2H, m, Ar), 5.79 (1H, s, 6-H); Mass: *m/z* 230; Anal. Calcd. for $C_{11}H_{10}N_4S$; C, 57.39; H 4.35; N, 24.35; S 13.91. Found: C, 57.77, H 4.22; N, 24.56%.

1,3,6-Triphenyl-4-amino-5-cyano-2-thiocytosine 3b : m.p. 199-203ºC; IR (KBr): 3429, 3202, 3153,



A



B

3087, 2233, 1608, 1547, 1229, 1148, 860 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 11.85 (2H, br s, NH_2, exchangeable with D_2O), 7.79-7.82 (6H, m, Ar), 7.35-7.42(9H, m, Ar), 4.58 (1H, s, 6-H); Mass: *m/z* 382; Anal. Calcd. for $C_{23}H_{18}N_4S$; C, 72.25; H 4.71; N, 14.66; S 8.38. Found: C, 72.34, H 4.87; N, 14.81%.

1,3-Bis(4-methoxyphenyl)-6-phenyl-2-thiocytosine 3c : m.p. 118-120ºC; IR (KBr): 3334, 3127, 2959, 2238, 1596, 1609, 1161, 1023, 755 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.55-7.65 (2H, m, Ar), 7.20-7.40 (7H, m, Ar), 6.92-7.10 (4H, m, Ar), 5.25 (1H, m, 6-H), 3.71 (6H, s, 2 × OMe); Mass: *m/z* 442; Anal. Calcd. for $C_{25}H_{22}N_4O_2S$; C, 67.87; H 4.98; N, 12.67; S 7.24. Found: C, 67.96, H 5.01; N, 12.71%.

1,3-Bis(4-methylphenyl)-6-phenyl-2-thiocytosine 3d : m.p. 168-170ºC; IR (KBr): 3238, 2985, 1565, 1240, 790 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.60-7.33 (5H, m, Ar), 7.02 (4H, br s, Ar), 6.80 (4H, br s, Ar), 5.12 (1H, s, 6-H), 2.22 (6H,s, 2 × CH_3); Mass: *m/z* 410; Anal. Calcd. for $C_{25}H_{22}N_4S$; C, 73.17; H 5.36; N, 13.67; S 7.80. Found: C, 73.25, H 5.47; N, 13.77%.

1,3-Bis(4-chlorophenyl)-6-phenyl-2-thiocytosine 3e : m.p. 158-160ºC; IR (KBr): 3173, 3018, 2228, 1613, 1533, 1317, 1168, 1096, 825, 729 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.28-7.55 (m, 13H, Ar), 5.36 (1H, s, 6-H); Mass: *m/z* 451; Anal. Calcd. for $C_{23}H_{16}N_4SCl_2$; C, 61.19; H 3.55; N, 12.42; S 7.09. Found: C, 61.29, H 3.61; N, 12.48%.

Typical procedure for the synthesis of thiouracils. A solution of ethyl phenylmethylenecyanoacetate (308 mg, 2 mmoles) and N,N-diphenylthiourea (2.5 mmoles) in acetonitrile (20 mL)-water (5 mL) was stirred at room temperature in the presence of KOH (0.5 g) and chromium(III) chloride (20 mol%) for 24 hr (TLC). The reaction mixture was poured onto crushed ice (20 g) and the solid product separated was filtered under suction, washed with cold water (20 mL) and then recrystallized from ethanol to afford 6-phenyl-5-cyano-2-thiouracil **4a**; m.p. 170-172ºC; IR (KBr): 3241, 1637 cm^{-1}; ^1H NMR (CD_3OD): δ 8.35 (1H, s, 6-H), 8.05-8.08 (2H, m, Ar), 7.50-7.68 (3H, m, Ar), 5.15 (1H, br s, 6-H); ^{13}C NMR (CD_3OD): δ 163.80, 154.83, 133.10, 131.98, 130.83, 129.19, 115.67, 103.68; Mass: *m/z* 231; Anal. Calcd. for $C_{11}H_9N_3OS$; C, 57.14; H 3.90; N, 18.18; S 13.85. Found: C, 57.21, H 3.93; N, 18.22%.

1,3,6-Triphenyl-5-cyano-2-thiouracil 4b : m.p. 188-190ºC; IR (KBr): 3429, 3202, 3153, 3087, 2233, 1608, 1547, 1229, 1148, 860 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.79-7.82 (6H, m, Ar), 7.35-7.42(9H, m, Ar), 4.55 (1H, s, 6-H); Mass: *m/z* 383; Anal. Calcd. for $C_{23}H_{17}N_3OS$; C, 72.06; H 4.44; N,10.97; S 8.36. Found: C, 72.15, H 4.56; N, 11.01%.

1,3-Bis(4-methoxyphenyl)-6-phenyl-2-thiouracil 4c : m.p. 199-203ºC; IR (KBr): 3241, 1637 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.65-7.35 (m, 5H), 7.15 (d, 4H, J = 8.6 Hz), 6.88 (d, 4H, J = 8.5 Hz), 5.09 (1H, s, 6-H), 3.48(6H, s, 2 × OMe); Mass: *m/z* 443; Anal. Calcd. for $C_{25}H_{21}N_3O_3S$; C, 67.72; H 4.74; N, 9.48; S 7.22. Found: C, 67.77, H 4.76; N, 9.56%.

1,3-Bis(4-methylphenyl)-6-phenyl-2-thiouracil 4d : m.p. 172-174ºC; IR (KBr): 3238, 2985, 1565, 1240, 790 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.60-7.33 (m, 5H), 7.02 (d, 4H, J = 8.6 Hz), 6.80 (d, 4H, J = 8.5 Hz), 5.12 (1H, s, 6-H), 2.34 (6H,s, 2 × CH_3); Mass: *m/z* 411; Anal. Calcd. for $C_{25}H_{21}N_3OS$; C, 73.00; H 5.11; N, 10.22; S 7.78. Found: C, 73.08, H 5.12; N, 10.56%.

1,3-Bis(4-chlorophenyl)-6-phenyl-2-thiouracil 4e : m.p. 168-170ºC; IR (KBr): 3238, 2985, 1565, 1240, 790 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.55-7.40 (m, 5H), 7.13 (d,4H, J = 8.6 Hz), 7.02 (d, 2H, J = 8.5 Hz), 5.36 (1H, s, 6-H); Mass: *m/z* 452; Anal. Calcd. for $C_{23}H_{15}N_3OSCl_2$; C, 61.06; H 3.32; N, 9.29; S 7.08. Found: C, 61.17, H 3.38; N, 9.56%.

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