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

Nimalini D Moirangthem & Warjeet S Laitonjam*
Department of Chemistry, Manipur University, Canchipur 795 003, Manipur, India
Email : warjeet@yahoo.com

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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 antithyroid activity in rats than pyrimidine-2-thiones itself. Pyrimidine-2-thiones and their derivatives are also known to exhibit biological activities, such as antiviral, antitumor, antibacterial, anti-inflammatory, antihypertension, etc. The condensation of thiourea and ethyl ethoxymethylene cyanoacetate was reported by Ulbricht and Price 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.

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 and several improved procedures have recently been reported. 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, 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 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 CH₃CN-H₂O (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 ¹H NMR and moreover, can avoid using harmful organic solvents.

Ethyl phenylmethylene enamalonitrile reacted with N-aryltioureas to give excellent yields of 4-aryltioureas to give excellent yields of 4-amino-5-cyano-6-phenyl-pyrimidine-2-thiones, which are derived from the intermediates 6-phenyl-2-thiocytosines. However, when ethyl phenylmethylene cyanoacetate was allowed to react with 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, which are derived from 6-phenyl-2-thiouracils, 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. A possible reason is seen for the formation of thiouracils rather than thiocytosines, when the intermediates in
these reactions are considered. Intermediates in reactions of this type were shown to be ureido-
methylenecyanoacetates 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$_2$Et 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-thiocytos-
sines. 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 evapo-
ration of a chloroform solution) on a sodium chloride
plate. Absorption maxima were recorded in wave
numbers (cm$^{-1}$). Proton nuclear magnetic resonance
($^1$H 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 ($\delta_H$ and
$\delta_C$) are quoted in parts per million (ppm) downfield
from tetramethyl silane (TMS). All samples were run
in deuto-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 phenylenemalono
mtrile (308 mg, 2 mmoles) and N,N-diphenyl-
thiourea (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. 190-192$^\circ$C; IR (KBr):
3479, 3339, 3223, 2220, 1634, 1531, 1298, 1242, 1160,
768 cm$^{-1}$; $^1$H NMR (CDCl$_3$+DMSO-d$_6$): $\delta$ 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. Caled. for
C$_{11}$H$_{10}$N$_4$S; 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. 199-203$^\circ$C; IR (KBr): 3429, 3202, 3153,
3087, 2233, 1608, 1148, 860 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): δ 11.85 (2H, br s, NH₂, exchangeable with D₂O), 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 C₂₃H₁₈N₄S; 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. 118-120°C; IR (KBr): 3334, 3127, 2959, 2238, 1596, 1609, 1161, 1023, 755 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): 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 C₂₅H₂₂N₄O₂S; 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-thiouracil 3d: m.p. 168-170°C; IR (KBr): 3238, 2985, 1565, 1240, 790 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): 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 × CH₃); Mass: m/z 410; Anal. Calcd. for C₂₅H₂₁N₃OS; C, 73.17; H 5.36; N, 13.67; S 7.24. Found: C, 73.25, H 5.47; N, 13.77%.

1,3-Bis(4-chlorophenyl)-6-phenyl-2-thiouracil 3e: m.p. 172-174°C; IR (KBr): 3238, 2985, 1565, 1240, 790 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): 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 C₂₅H₂₁N₃OS; C, 76.72; H 4.74; N, 9.48; S 7.22. Found: C, 76.77, H 4.76; N, 9.56%.

Typical procedure for the synthesis of thiouracils. A solution of ethyl phenylmethyleneacetate (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. 170-172°C; IR (KBr): 3241, 1637 cm⁻¹; ¹H NMR (CD₂OD): 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); ¹³C NMR (CD₂OD): δ 163.80, 154.83, 133.10, 131.98, 130.83, 129.19, 115.67, 103.68; Mass: m/z 231; Anal. Calcd. for C₁₁H₉N₃OS; 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. 188-190°C; IR (KBr): 3429, 3202, 3153, 3087, 2233, 1608, 1547, 1148, 860 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): 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 C₂₃H₁₇N₃OS; 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. 199-203°C; IR (KBr): 3241, 1637 cm⁻¹; ¹H NMR (CDCl₃+DMSO-d₆): 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 C₂₅H₂₁N₃O₃S; C, 67.72; H 4.74; N, 9.48; S 7.22. Found: C, 67.77, H 4.76; N, 9.56%.

References