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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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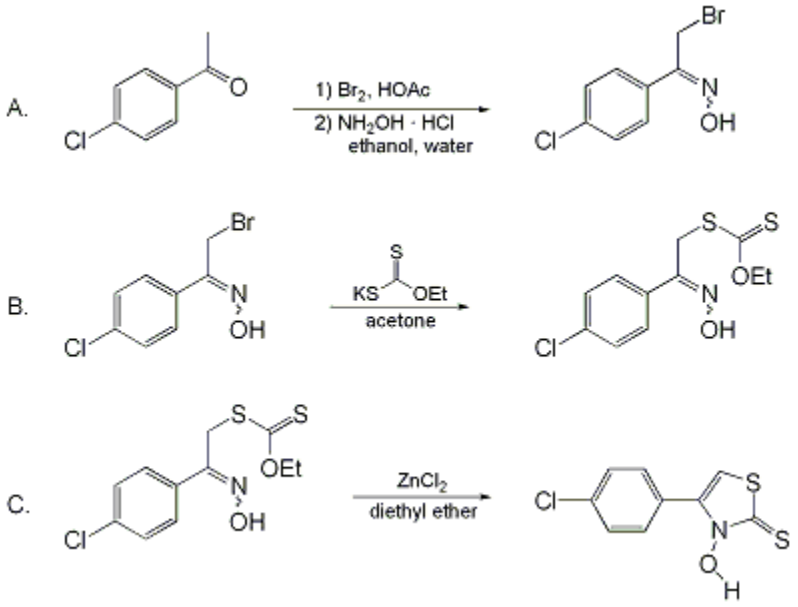
N-HYDROXY-4-(p-CHLOROPHENYL)THIAZOLE-2(3H)-THIONE

[2(3H)-Thiazolethione, 4-(4-chlorophenyl)-3-hydroxy-]



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Checked by Raghuram S. Tangirala and Dennis P. Curran.
Discussion Addendum *Org. Synth.* **2012**, *89*, 409

1. Procedure

A. ω-Bromo-p-chloroacetophenone oxime . A 500-mL, four-necked, round-bottomed flask equipped with a dropping funnel (closed with a glass stopper), mechanical stirrer, drying tube (calcium chloride, $CaCl_2$), and a thermometer is charged with p-chloroacetophenone (38.6 g, 0.25 mol), glacial acetic acid (220 mL) and aqueous hydrobromic acid (HBr) [1 mL, 48% (w/w), Note 1]. The flask is immersed in a water bath (15°C, Note 2) and bromine (40.0 g, 0.25 mol) is added from the dropping funnel at such a rate that the temperature of the reaction mixture does not exceed 25°C (Note 3). Stirring is continued for 1 hr at 15°C. The suspension is poured onto 1 kg of crushed ice. The colorless precipitate is collected by suction (Buchner funnel) and repeatedly washed with small portions of water (total of 200 mL). Approximately 84 g of air-dried ω-bromo-p-chloroacetophenone is obtained from this step (Note 4). The crude product is transferred into a 1-L beaker that is equipped with a magnetic stirring bar (Note 5). Aqueous ethanol (96%, v/v, 400 mL) is added and the slurry is treated with a solution of hydroxylamine hydrochloride [21.7 g, 0.31 mol, (Note 6)] in water (65 mL) in one portion at 20°C. Stirring is continued for 24 hr at 20°C to afford a clear, pale yellow solution that is poured onto a mixture of ice (900 g) and water (400 mL). ω-Bromo-p-chloroacetophenone oxime separates as a colorless solid that is collected by filtration on a Buchner funnel. The precipitate is washed with small portions of water (total of 200 mL) and dried for 48 hr at 20°C and 10^{-3} mbar (7.5×10^{-4} mm) to furnish 53 g (85.3%) of ω-bromo-p-chloroacetophenone oxime as a colorless powder (Note 7).

B. O-Ethyl S-[oximino-2-(p-chlorophenyl)ethyl]dithiocarbonate . A 1-L, round-bottomed flask equipped with a dropping funnel is charged with a magnetic stirring bar, potassium O-ethyl xanthate (35.3 g, 0.22 mol), and acetone (140 mL). A solution of ω-bromo-p-chloroacetophenone oxime (49.5 g, 0.20 mol) in acetone (120 mL) is added dropwise at room temperature over a period of 30 min. Stirring is continued for 3 hr at 20°C whereupon a cloudy orange solution forms from the initial slurry. Solids are removed by filtration using a thin pad of diatomaceous earth (1-cm height in a Buchner funnel) to afford a clear orange solution. The solids on the funnel are washed with acetone (total of 50 mL). The combined washings and filtrate are concentrated under an aspirator vacuum to dryness to furnish a

yellow residue that is dissolved in diethyl ether (750 mL). This solution is washed with water (200 mL), dried (magnesium sulfate, $MgSO_4$), and evaporated to dryness to afford 51.9 g (89.5%) of O-ethyl S-[2-oximino-2-(p-chlorophenyl)ethyl]dithiocarbonate as a yellow amorphous solid.

C. N-Hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione . O-Ethyl S-[2-oximino-2-(p-chlorophenyl) ethyl]dithiocarbonate (56.0 g, 0.19 mol) is placed in a 500-mL round-bottomed flask that is equipped with a magnetic stir bar. Diethyl ether (120 mL) is added and the slurry is treated at 0°C in small portions with solid anhydrous zinc chloride , $ZnCl_2$, 79.1 g, 0.58 mol) at such a rate that the solvent does not boil constantly (Note 8). After the addition is complete, the flask is stoppered with a drying tube ($CaCl_2$) and stirring is continued for 48 hr at 20°C. The reaction mixture turns into a clear, dark brown solution that solidifies toward the end of the reaction. The flask is immersed in an ice bath and treated dropwise with 5.5 M hydrochloric acid (140 mL, Note 9). The precipitate dissolves immediately. Stirring is continued for 30 min at 0°C whereupon a tan-colored solid separates. This material is collected by filtration. It is washed with small portions of diethyl ether (total of 110 mL) and dried to afford 39.8 g (86%) of N-hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione (Note 10). The crude material is transferred to a 2-L, round-bottomed flask equipped with a reflux condenser. 2-Propanol (760 mL) is added and the reaction mixture is heated to reflux. Once a clear solution is obtained the heat source is immediately removed (Note 11). The solution is allowed to cool to room temperature. Precipitation of N-hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione is completed by immersing the flask for 30 min in an acetone-dry ice bath (−78°C). The product is collected by filtration and dried to afford 21.9 g (53.5%) of N-hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione as tan crystals (Notes 12, 13).

2. Notes

1. A three-necked, round-bottomed flask with Claisen head may be used instead. p-Chloroacetophenone (97%), hydroxylamine hydrochloride (purum p.a. ≥98%), potassium O-ethyl xanthogenate (≥98%), bromine (puriss. p.a., ≥99.5%), and hydrobromic acid [puriss. 48% (w/w)] were obtained from Fluka Chemika and used as received. All solvents [acetic acid (reagent grade, 99-100%, Merck & Company, Inc.), diethyl ether (purum, ≥99%, stabilized with 0.0001% of 2,6-di-tert-butyl-p-cresol, Fluka Chemika), acetone (purum, ≥99%, Fluka Chemika), 2-propanol (purum, ≥99%, Fluka Chemika), and ethanol (purum, 96%, 2% ethyl methyl ketone, and 0.5% isobutyl methyl ketone, Fluka Chemika)] were used without further purification. Zinc chloride was used as received from Riedel de Haen (puriss., 98-100%).
2. The temperature of the reaction mixture is kept at 15°C throughout the reaction by adding portions of crushed ice to the water bath. If the temperature drops below 10°C the solvent starts to solidify; above 25°C products of dibromination are formed.
3. Bromine should be handled in a well-ventilated hood. Addition of bromine usually is complete within 75 min.
4. ω-Bromo-p-chloroacetophenone was used without further drying in the oxime-forming reaction. Drying of this product from step (A) at 20°C and 10^{-3} mbar (7.5×10^{-4} mm) affords 58.3 g of ω-bromo-p-chloroacetophenone . ω-Bromoacetophenones are lachrymators. Skin contact should be avoided.
5. A 4-cm stirring bar is adequate.
6. The two reactions in Step A were taken from the literature[2] [3] and were improved for the present synthesis. All previously related syntheses of arylacetophenone oximes found in the literature have used a threefold excess of hydroxylamine hydrochloride that is, however, not necessary in the present protocol.
7. Drying ω-bromo-p-chloroacetophenone oxime was carried out in the dark since otherwise this material turns pink in light. Wrapping the flask with aluminum foil provides adequate light protection for this purpose.
8. Addition of $ZnCl_2$ is exothermic. The reaction mixture may bubble upon addition of each portion of $ZnCl_2$, but it should not boil constantly. After addition of $ZnCl_2$ is complete, a 4.8-5 M solution of $ZnCl_2$ is obtained that leads to a maximum yield of the title compound. It was essential to use diethyl ether as solvent in this step. Also no excess diethyl ether should be added after the addition of $ZnCl_2$ is complete.
9. 5.5 M Hydrochloric acid was prepared from 80 mL of concentrated hydrochloric acid and 60 mL of water. This step should be carried out in a well-ventilated hood since an unpleasant smell develops.
10. To some people, N-hydroxy-4-(p-chlorophenyl)-thiazole-2(3H)-thione has a musty odor. Thus, the

submitters recommend that the compound be handled and stored in a ventilated place. All drying operations in Step C were carried out at 20°C/10^{-2} mbar (7.5×10^{-3} mm). If prolonged storage of the title compound is required, the use of an amber-colored vial is recommended.

11. The solution should not be heated longer than necessary to obtain a clear solution. According to differential thermal analysis, neat N-hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione decomposes at 138 ± 2°C without melting.

12. Analytical data for N-hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione is as follows: IR (CCl_4) cm^{-1}: 3124, 2942, 1603, 1581, 1556, 1500, 1488, 1404, 1355, 1301, 1214, 1174, 1095, 1062, 1016, 976 ; UV/Vis (EtOH) λ_{max} (log ε): 309 (4.16), 240 nm (4.20) ; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.68 (s, 1 H), 7.47 (m_c, 2 H), 7.62 (m_c, 2 H), 11.72 (br s, 1 H, OH) ; ^{13}C NMR (100 MHz, (DMSO-d_6) δ: 106.4, 127.6, 128.7, 130.1, 134.4, 140.3, 179.2 ; Anal. Calcd for $C_9H_6ClNOS_2$ (243.7): C, 44.35; H, 2.48; N, 5.75; S, 26.31. Found: C, 44.35; H, 2.47; N, 5.74; S, 26.39.

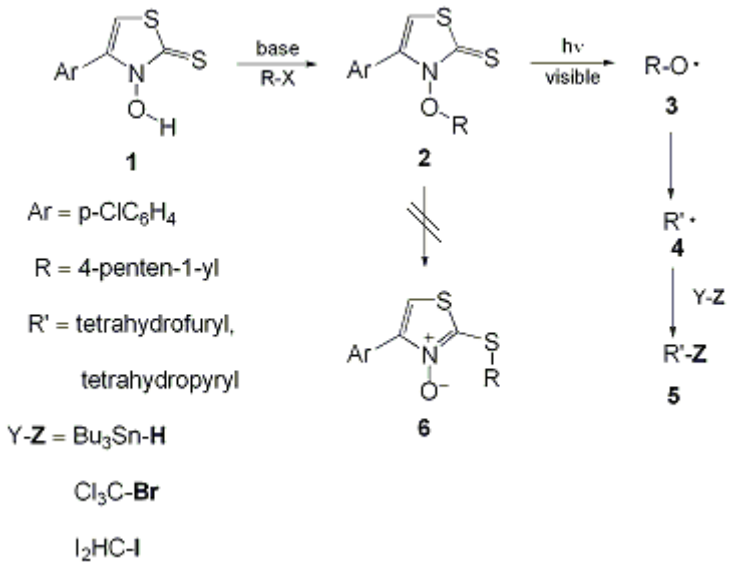
13. The submitters report that a second crop of the title compound (7.7 g, 16%) of similar quality separates from the mother liquor upon concentration of the volume of the solution to 100 mL and storage at −20°C overnight. This was not checked.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

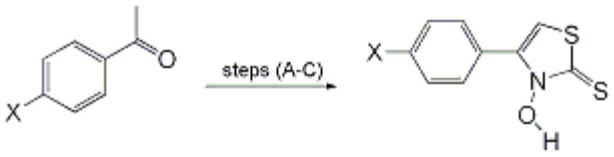
3. Discussion

N-Hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione (**1**) is a valuable starting material for the synthesis of N-alkoxy derivatives **2** by a number of well-elaborated O-alkylation procedures (Figure 1).[4] [5]



Substituted heterocycles **2** serve as sources of oxygen-centered radicals **3** for mechanistic and synthetic purposes. This method was recently applied as a key step in the synthesis of a muscarine alkaloid.[6] N-Alkoxy-4-(p-chlorophenyl)thiazole-2(3H)-thiones **2** offer significant advantages compared with their best current alternatives, the N-alkoxypyridine-2(1H)-thiones[7] [8] since they combine two rare properties required for efficient radical precursors. On the one hand they are sufficiently stable to allow safe handling and storage in standard glassware without being prone to photochemical decomposition or to thermal rearrangement, **2** → **6**. This O-alkyl → S-alkyl shift is a significant decomposition pathway for substituted N-benzylpyridine-2(1H)-thiones.[9] In contrast to their thermal stability, thiazolethiones **2** efficiently liberate oxygen-centered radicals **3** in chain reactions upon photolysis.[4] In this sense, N-alkoxy-4-(p-chlorophenyl)thiazole-2(3H)-thiones are superior to many existing alkoxyl radical precursors.

A smaller scale and less efficient synthesis of the phenyl derivative of **1** has been reported.[10] The method described for the title compound **1** provides excellent synthetic access to the p-chlorophenyl-substituted thiazolethione **1**. It offers higher yields in every step of the synthesis, reduces the amount of hydroxylamine hydrochloride used in Step A to a third and avoids the use of halogenated solvents and methanol. Further, only one purification step is necessary at the very end of the synthesis to afford pure thione **1**. The protocol for N-hydroxy-4-(p-chlorophenyl) thiazole-2(3H)-thione has also been applied to syntheses of the respective p-substituted phenyl derivatives **7-9** [4] from the respective acetophenones (Figure 2)



X	Compound	Yield
OCH_3	**7**	46%
CH_3	**8**	49%
Cl	**1**	67%
NO_2	**9**	42%

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-Hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione:
2(3H)-Thiazolethione, 4-(4-chlorophenyl)-3-hydroxy- (11); (105922-93-8)

ω-Bromo-p-chloroacetophenone oxime:
Ethanone, 2-bromo-1-(4-chlorophenyl)- oxime (12); (136978-96-6)

p-Chloroacetophenone:
Ethanone, 1-(4-chlorophenyl)- (8,9); (99-91-2)

Hydrobromic acid (8,9); (10035-10-6)

Bromine (8,9); (7726-95-6)

Hydroxylamine hydrochoride (8);
Hydroxylamine, hydrochloride (9); (5470-11-1)

O-Ethyl S-[oximino-2-(p-chlorophenyl)ethyl]dithiocarbonate:
Carbonodithioic acid, S-[2-(4-chlorophenyl)-2-(hydroximino)ethyl], O-ethyl ester (14); (195213-53-7)

Potassium O-ethyl xanthate or
Potassium O-ethyl xanthogenate:
Carbonodithioic acid O-ethyl ester, potassium salt (8,9); (140-89-6)

Zinc chloride (8,9); (7646-85-7)