Simple and Efficient Preparation of Reagents for Thiopyran Introduction: Methyl Tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate, Tetrahydro-4*H*-thiopyran-4-one, and 3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyran

Dale E. Ward,* M. Abdul Rasheed, H. Martin Gillis, Garrison E. Beye, Vishal Jheengut, George T. Achonduh

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK, S7N 5C9, Canada
Fax +1(306)9664730; E-mail: dale.ward@usask.ca

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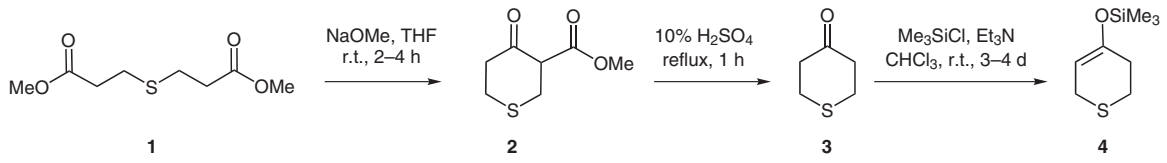
Abstract: Tetrahydro-4*H*-thiopyran-4-one was prepared in >75% yield by treatment of dimethyl 3,3′-thiobispropanoate with NaOMe (generated in situ) in THF solution and decarboxylation of the resulting methyl tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate in refluxing 10% aqueous H_2SO_4. Reaction of tetrahydro-4*H*-thiopyran-4-one with Me_3SiCl and Et_3N in $CHCl_3$ gave the corresponding trimethylsilyl enol ether in near quantitative yield. The prepared reagents are useful for the synthesis of thiopyran-containing compounds.

Key words: tetrahydro-4*H*-thiopyran-4-one, 4-thianone, heterocyclic ketone, Dieckmann cyclization, thiopyran synthesis



Scheme 1

Cyclic sulfides are an important class of compounds with numerous applications in many areas of chemistry.[1] In particular, thiopyran-derived scaffolds have been exploited in diverse ways.[2] The synthesis of such targets often involves the elaboration of simple thiopyran-containing reagents such as **2**–**4**.[3] Of these, only tetrahydro-4*H*-thiopyran-4-one (**3**) is commercially available, albeit at a significant cost.[4] We have been investigating aldol reactions of **3** for the rapid assembly of stereochemically diverse polypropionate synthons and required large amounts of **2** and **3** for this purpose.[5] Herein we report simple and cost-efficient procedures for the preparation of **2**, **3**, and **4** (Scheme 1).

Several methods for the synthesis of **3** are known,[3,6–9] most commonly by the decarboxylation of **2**.[7–9] The β-keto ester **2** is also a versatile reagent for synthesis of thiopyran-containing compounds and numerous reports on its preparation by Dieckmann cyclization of **1**[10] or an analogous diester have been published.[7,8,11] Most of these methods involve the use of NaOMe or NaH in various modifications of Fehnel and Carmack's improvement of the original procedure by Bennet and Scorah.[7] Compared to the Fehnel and Carmack protocol (2 equiv of 'alcohol-free' NaOMe in refluxing diethyl ether; 64% yield of **2** on 1.4 mol scale), the modified procedures typically describe reactions on much smaller scale (<0.1 mol) and the reported yields vary widely (13–81%; most around 75%). The importance of the quality of the NaOMe used has been noted[9a] and it is likely that the diester **1** is susceptible to hydrolysis by small amounts of NaOH. It is known that the reaction is accompanied by some cleavage of the sulfide linkage in **1**, especially at higher temperatures, resulting in the formation of methyl 3-methoxypropionate, methyl 3-mercaptopropionate, and hydrogen sulfide.[9a] Our experiments indicate that **2** readily decomposes under basic conditions in protic solution, perhaps contributing to the high variation in the reported yields.

We previously reported a simplified procedure for the conversion of **1** into **2** (2 equiv of NaOMe in Et_2O–THF; 93 ± 5% on 0.5 mol scale).[5b] Subsequently, we optimized several reaction parameters and have now developed a very robust, scalable, and cost-effective procedure. The amount of NaOMe used can be reduced to 1.3 equivalents[12] and its quality is easily controlled with in situ generation by addition of anhydrous methanol to a suspension of Na metal in THF. Addition of **1** to the resulting NaOMe/THF mixture results in complete conversion to **2** in 2–4 hours at room temperature. The use of THF as solvent (compared to diethyl ether or benzene) is highly advantageous because it gives a homogenous reaction mixture, permits higher reaction concentrations (2.5 M in **1**), and results in shorter reaction times. Neutralization of the cold reaction mixture followed by standard aqueous work-up affords **2** in high yield (ca. 95%) (Scheme 1). On larger scales (>100 g of **1**) the above

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work-up involves processing a considerable amount of solvent. More conveniently, the reaction mixture can be quenched by addition of 50% H_2SO_4 (1.0 equiv of H^+ with respect to Na); simple filtration of the precipitated Na_2SO_4 hydrate and concentration gives **2** in 92–98% yield (0.1–0.6 kg scale).

The decarboxylation of **2** to give **3** can be achieved under basic conditions or more efficiently by refluxing in aqueous H_2SO_4.[7a] Several closely related procedures have appeared with reported yields varying from 60–91%.[7,8] Similarly, a number of 'one-pot' procedures (NaOMe then H_2SO_4) for preparation of **3** from **1** without isolation of the intermediate **2** have been described (39–58% overall yield).[9] In many of the reported procedures, the yields obtained represent 'crude' **3** of uncertain purity; 'pure' **3** (the mp reported varies from 58–60 to 65–67 °C) has been obtained by sublimation[6a] or recrystallization.[7a,8a–d,9c] We were unable to obtain good yields of pure **3** using any of the above procedures. The ketone **3** is quite volatile[7a] and readily sublimes even on a rotary evaporator (especially on heating). Also, the solubility of **3** in water is surprisingly high and the usual work up procedures involving aqueous washes necessarily reduce the yield. In control experiments, we established that **3** decomposes to unidentified products in refluxing aqueous H_2SO_4 at the rate of ca. 2–3% per hour and these products are not effectively removed by washing with aqueous base. Moreover, the decarboxylation of **2** in refluxing aqueous H_2SO_4 is much slower in the presence of Na_2SO_4 (i.e., as in the 'one-pot' procedures) or at higher concentrations (perhaps due to the limited solubility of **2** in water) and these slower decarboxylations produce a significantly greater amount of yellow oily by-products that complicate the purification of **3**. These results can help to explain the wide range in the yield of **3** obtained by various researchers.

We have found that adding **2** to ten times its mass of refluxing 10% aqueous H_2SO_4 leads to complete transformation to **3** within one hour. The remarkable water solubility of **3** provides a simple purification method. On cooling, a yellow oil separates from the reaction mixture and the oil is washed with warm water. The dichloromethane extracts of the combined aqueous layers are directly passed through a short pad of basic alumina (to remove the polar by-products) and concentrated to give white crystalline **3** of high purity in 76–80% yield (50–200 g scale) (Scheme 1).

Trialkylsilyl enol ethers of **3**, particularly **4**, are also useful reagents.[5b,13] These compounds have been prepared from **3** in yields of ca. 80% using the method of House et al.[14] (e.g., from reaction of the LDA-generated lithium enolate with Me_3SiCl).[13] We reported that **4** can be prepared in 95% yield by reaction of **3** with Me_3SiCl and Et_3N in CH_2Cl_2.[5b] The long reaction time (10 d) and large excess of reagents (5 equiv of Me_3SiCl) required in that procedure are disadvantages, especially on large scale. We have found that the reaction is considerably faster in $CHCl_3$ and goes to completion in 3–4 days with 1.5 equivalents of Me_3SiCl to give **4** in near quantitative yield (Scheme 1).

In summary, we have developed scalable, efficient, and cost-effective procedures for the preparation of **2**, **3**, and **4** from the commercially available and inexpensive **1**.[10] In view of already widespread use of **3** and its derivatives in synthesis, these procedures should facilitate additional applications.

Anhydrous solvents were distilled under argon as follows: THF from benzophenone sodium ketyl and MeOH from $Mg(OMe)_2$. Reagent grade $CHCl_3$ was passed through basic alumina prior to use; Et_3N and Me_3SiCl were distilled from CaH_2 and Bu_3N, respectively. All other reagents and solvents were commercially available and unless otherwise noted, were used as received. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator with the final traces of solvent removed at high vacuum (ca. 0.7 mbar). All reported compounds were homogenous by thin-layer chromatography (TLC) and ^1H NMR spectra.

Methyl Tetrahydro-4-oxo-2*H*-thiopyran-3-carboxylate (2)

Anhyd MeOH (41 mL, 32 g, 1.0 mol) was added via a dropping funnel over 30 min to a stirred suspension of Na metal (21.7 g, 0.95 mol)[15] in THF (300 mL) at 0 °C (ice bath) under argon (**Caution!** H_2 evolution). The ice bath was removed and stirring continued at r.t. for 15–20 h, at which point most of the Na was consumed (ca. 90%)[15] leaving a grayish-white mixture of NaOMe in THF. The mixture was cooled in an ice bath and the diester **1** (150 g, 0.728 mol) was added via a dropping funnel over 1 h (the dropping funnel was rinsed with 15 mL of THF). The ice bath was removed and the mixture, initially a thick slurry, became a homogeneous amber solution.[16] After stirring for 3 h at r.t., the reaction was complete by TLC analysis (30% EtOAc in hexane). The mixture was transferred to a beaker equipped with a mechanical stirrer and cooled in an ice bath. Aq H_2SO_4 (0.475 mol; prepared by adding 47.5 g of 98% H_2SO_4 to ca. 45 g of ice) was added slowly with stirring maintaining the temperature below 20 °C; the final pH was 6–7. To the resulting creamy yellow mixture, CH_2Cl_2 (400 mL) was added after which the Na_2SO_4 hydrate precipitated as granules that readily settle, leaving a pale yellow solution; occasionally, a small amount of H_2O (2–10 mL) must be added to achieve the desired consistency. Na_2SO_4 (20 g) and solid $NaHCO_3$ (21 g) were added with stirring and after 30 min, the supernatant was filtered through cotton wool and the residue was washed with CH_2Cl_2 (200 mL). The combined filtrate and washings were concentrated to give the titled compound as a pale yellow oil (*stench!*); yield: 124.5 g (98%); >95% purity[17] by NMR. The oil solidified (keto form) on standing for several days at 5 °C.

IR (diffuse reflectance): 3100 (br), 1745, 1720, 1658, 1617 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (for the enol tautomer) = 12.5 (s, 1 H), 3.79 (s, 3 H), 3.36 (s, 2 H), 2.80 (app t, *J* = 5.5 Hz, 2 H), 2.60 (app t, *J* = 5.5 Hz, 2 H); δ (for the keto tautomer) = 3.80 (s, 3 H), 3.70 (dd, *J* = 4, 8.5 Hz, 1 H), 3.31 (dd, *J* = 8.5, 14 Hz, 1 H), 3.06 (dd, *J* = 4, 14 Hz, 1 H), 2.99–2.94 (m, 2 H), 2.91–2.85 (m, 1 H), 2.77–2.72 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (for the enol tautomer) = 172.0, 169.3, 97.4, 51.9, 30.9, 24.6, 23.4; δ (for the keto tautomer) = 203.7, 172.6, 58.7, 52.7, 43.7, 32.6, 30.5.

HRMS-EI: *m/z* [M^+] calcd for $C_7H_{10}O_3S$: 174.0351; found: 174.0348.

Tetrahydro-4*H*-thiopyran-4-one (3)

Keto ester **2** (100 g, 0.57 mol) was added via a dropping funnel over 3–5 min to a well-stirred solution of 10% aq H_2SO_4 (1 L) heated un-

der reflux. After ca. 1 h, the reaction was complete by TLC analysis (30% EtOAc in hexane) and the mixture was cooled to 40 °C with the aid of an ice bath. The aqueous layer was decanted from a yellow oil that separated and settled. The yellow oil was washed with H_2O (500 mL) at 40 °C and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 200 mL) with each extract passed through a column of basic Al_2O_3 (Brockmann I, ca. 150 mesh; 200 g). The column was finally eluted with CH_2Cl_2 (600 mL) and the combined eluates were concentrated and then reconcentrated from hexane to give the titled compound as a white, freely flowing, crystalline solid (52 g, 78%); mp 59–60 °C.

IR (diffuse reflectance): 1704 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.99–2.94 (m, 4 H), 2.72–2.68 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 44.7, 30.6.

HRMS-EI: *m/z* [M^+] calcd for C_5H_8OS: 116.0296; found: 116.0293.

3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyran (4)

Et_3N (27.8 mL, 20.2 g, 0.20 mol) and Me_3SiCl (19.2 mL, 16.3 g, 0.15 mol) were sequentially added to a stirred solution of **3** (11.6 g, 0.10 mol) in $CHCl_3$ (116 mL) under argon and the mixture was allowed to stand in the dark at r.t. in a well-stoppered flask. The reaction progress was monitored by ^1H NMR (a small sample was withdrawn and processed as described below) and when complete (3–4 d), the mixture was concentrated, diluted with hexane (200 mL), and filtered through Celite. The combined filtrate and hexane washings were concentrated to give **3** as yellow oil (18.4 g, 98% yield) that was homogenous by ^1H NMR spectrum and was used without further purification. The material slowly decomposed (mainly by hydrolysis) upon storage under argon even at –15 °C. If not used promptly, a convenient method[5b] of storage involves making a solution of known concentration in benzene (ca. 1 M) containing Et_3N (2 equiv). This solution can be stored for at least three months at –15 °C with negligible decomposition. The product is recovered as required by concentrating aliquots.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.06–5.04 (m, 1 H), 3.15–3.14 (m, 2 H), 2.76–2.72 (m, 2 H), 2.27–2.23 (m, 2 H), 0.17 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.3, 102.2, 31.2, 25.7, 25.1, 0.3.

HRMS-EI: *m/z* [M^+] calcd for $C_8H_{16}OSSi$: 188.0708; found: 188.0705.

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(15) Na metal was cut into pieces weighing ca. 50–100 mg (3–5 mm per side). The rate of Na consumption depends on the size of pieces; with larger pieces, more time is required to reach 90% conversion.

(16) A few specks of Na metal may remain at this point.

(17) The presence of small amounts of **1** (<1%) and its corresponding half-acid (1–2%) were detected by ^{13}C NMR and confirmed by spiking with authentic samples.