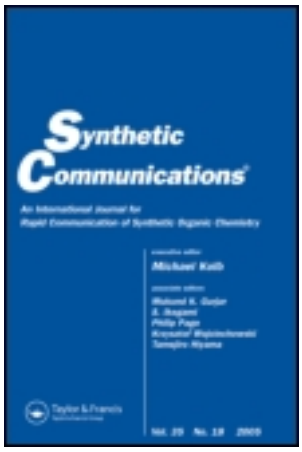

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Multigram Scale Synthesis of Tetrahydrothiophene-3-one-1,1-dioxide

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Version of record first published: 16 Aug 2006

To cite this article: Robert J. Altenbach, Ladislav Kalvoda & William A. Carroll (2004): A Convenient Multigram Scale Synthesis of Tetrahydrothiophene-3-one-1,1-dioxide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:4, 567-570

To link to this article: http://dx.doi.org/10.1081/SCC-120027703

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 4, pp. 567–570, 2004

A Convenient Multigram Scale Synthesis of Tetrahydrothiophene-3-one-1,1-dioxide

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ABSTRACT

A short and efficient multigram scale synthesis of tetrahydrothiophene-3-one-1,1-dioxide is described.

Key Words: Tetrahydrothiophene-3-one-1,1-dioxide; Sulfone; Mole-scale two pot synthesis.

We recently required multigram quantities of tetrahydrothiophene-3-one-1,1-dioxide (**3a**) for the synthesis of sulfone containing dihydropyridines. We have developed a mole scale synthesis of **3a** from commercially available

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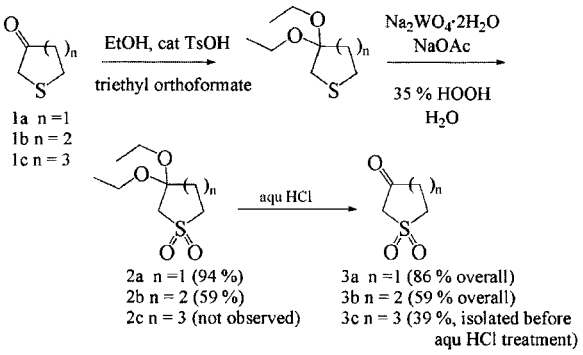
DOI: 10.1081/SCC-120027703 0039-7911 (Print); 1532-2432 (Online)



Scheme 1. Synthesis of ketosulfones **3a**–**3c**.

tetrahydrothiophen-3-one (**1a**) that is an alternative to existing published methods.[1,2]

The synthesis of compound **3a** is illustrated in Sch. 1. Tetrahydrothiophene-3-one (**1a**, 101 g, 1.05 mol) was protected as the diethyl ketal using triethyl orthoformate in the presence of para-toluenesulfonic acid and then directly oxidized with aqueous hydrogen peroxide in the presence of a catalytic amount of sodium tungstate and sodium acetate. The crystalline product was isolated by filtration and washed with water. This one pot process yielded 195 g (94%) of intermediate **2a**. Deprotection of **2a** in aqueous acid provided, after crystallization from ethanol, 116 g (86% overall yield) of the desired tetrahydrothiophene-3-one-1,1-dioxide (**3a**).

The key step in this process is the generation of intermediate **2a** via the one pot diethyl ketal formation and tungsten catalyzed oxidation of commercially available tetrahydrothiophen-3-one (**1a**). Belletire and Spletzer arrived at a similar intermediate via reaction of 3,4-dibromotetrahydrothiophene-1,1-dioxide with excess sodium methoxide in methanol.[1] Miklos and Senning generated a spiro ketal version of intermediate **2a** using a two step process.[3] The advantage of our method is that **2a** can be isolated on large scale simply by filtration and the overall process of generating **3a** is higher yielding. The use of toxic oxidants such as Jones reagent is also avoided.[2]

To investigate the scope of this process, the six and seven membered ring thiopyran-3-one (**1b**)[4] and thiepan-3-one (**1c**)[4] were subjected to the above sequence. The one pot protection/oxidation of **1b** provided the intermediate diethyl ketal sulfone **2b** in 59%. Deprotection of **2b** provided **3b** in a quantitative yield. In the case of **1c**, the protection/oxidation step did not yield the intermediate ketal **2c**. Instead, a 39% yield of **3c** was directly obtained. The lower yield of **2b** and the lack of isolation of **2c** under these reaction

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conditions may be a result of intermediates **2b** and **2c** being less stable and possibly less crystalline than **2a**.

In summary, we have developed a convenient and efficient mole-scale two pot synthesis of **3a** from commercially available **1a**. This sequence requires no chromatography and avoids the use of cumbersome and environmentally hazardous oxidants such as Jones reagent.

EXPERIMENTAL SECTION

Proton NMR spectra were obtained on a General Electric QE 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Thin layer chromatography (TLC) was performed using 250 μm silica gel 60 glassbacked plates with F_{254} as indicator.

3,3-Diethoxytetrahydrothiophene-1,1-dione (2a). A mixture of tetrahydrothiophen-3-one (**1a**, 101 g, 1 mol), ethanol (20 mL) and triethyl orthoformate (155 g, 1.05 mol) was treated with *p*-toluenesulfonic acid (0.5 g, 0.0026 mol) and stirred for 20 hours. The mixture was treated with anhydrous sodium acetate (3.3 g, 0.04 mol), sodium tungstate dihydrate (2.8 g, 0.0085 mmol) and water (280 mL). A 35% solution of hydrogen peroxide in water (285 mL) was added dropwise while keeping the mixture cooled to 30°C. After stirring over night at ambient temperature, the resulting crystalline product was collected by filtration, washed with water and dried (not necessary for the next step) to provide 195 g (94%) of 3,3-diethoxytetrahydrothiophene-1,1-dione. m.p. 80–82°C; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 6H, $J = 7.1$ Hz), 2.43 (t, 2H, $J = 7.2$ Hz), 3.22 (t, 2H, $J = 7.4$ Hz), 3.30 (d, 2H, $J = 0.9$ Hz), 3.52 (m, 4H); MS (DCI/NH_3) m/z 226 $(M + NH_4)^+$; Anal. Calcd. for $C_8H_{16}O_4S$: C, 46.13; H, 7.74; S, 15.40. Found: C, 46.30; H, 7.54; S, 15.41.

Tetrahydrothiophene-3-one-1,1-dioxide (3a). A suspension of compound **2a** (195 g, 0.94 mol) in a mixture of concentrated HCl (6 mL) and water (600 mL) was stirred at 60°C for 2 hours. The mixture was concentrated to a thick syrup and treated with dichloromethane (600 mL). The dichloromethane layer was isolated, dried ($MgSO_4$), filtered and concentrated. The residue was crystallized from hot ethanol (150 mL). The resulting crystals were collected by filtration, washed with ethanol and dried to provide 116 g (86% overall) of tetrahydrothiophene-3-one-1,1-dioxide. m.p. 60–62°C; ^{1}H NMR ($CDCl_3$) δ 3.0 (d, 2H, $J = 7.9$ Hz), 3.58 (m, 2H), 3.71 (s, 2H); MS (DCI/NH_3) m/z 152

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$(M + NH_4)^+$; Anal. Calcd. for $C_4H_6O_3S$: C, 35.81; H, 4.51; S, 23.90. Found: C, 36.18; H, 4.20; S, 23.75.

3,3-Diethoxytetrahydrothiopyran-1,1-dione (2b). Dihydrothiopyran-3-one[4] (**1b**, 5.0 g, 43 mmol) provided 5.7 g (59%) of 3,3-diethoxytetrahydrothiopyran-1,1-dione. A 30% solution of hydrogen peroxide in water was used in place of the 35% solution. m.p. 96–97°C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 6H, $J = 7$ Hz), 1.88 (m, 2H), 2.11 (m, 2H), 2.98 (m, 2H), 3.25 (s, 2H), 3.44–3.60 (m, 4H); MS (DCI/NH_3) m/z 240 $(M + NH_4)^+$; Anal. Calcd. for $C_9H_{18}O_4S$: C, 48.63; H, 8.16; S, 14.42. Found: C, 48.69; H, 7.97; S, 14.33.

Tetrahydrothiopyran-3-one-1,1-dioxide (2c). Compound **2b** (3.3 g, 15 mmol) provided 2.2 g (99%) of tetrahydrothiopyran-3-one-1,1-dioxide. m.p. 139–141°C; ^{1}H NMR (DMSO-d_6) δ 2.00 (m, 2H), 2.54 (m, 2H), 3.44 (m, 2H), 4.28 (s, 2H); MS (DCI/NH_3) m/z 166 $(M + NH_4)^+$; Anal. Calcd. for $C_5H_8O_3S$: C, 40.53; H, 5.44; S, 21.64. Found: C, 40.43; H, 5.43; S, 21.63.

Thiepan-3-one-1,1-dioxide (3c). Thiepan-3-one[4] (**1c**, 2.5 g, 19 mmol), ethanol (1.14 mL) and triethyl orthoformate (7.2 g, 48 mmol) were treated with *p*-toluenesulfonic acid (37 mg, 0.19 mmol) and stirred for 44 hours. The mixture was treated with anhydrous sodium acetate (64 mg, 0.8 mmol), treated with sodium tungstate dihydrate (54 mg, 0.16 mmol), treated with H_2O (5.5 mL) and treated dropwise with 30% hydrogen peroxide (7 mL, keeping the reaction temperature below 30°C during the addition) and stirred at ambient temperature for 60 hours. The precipitate was collected by filtration, washed with water and dried under vacuum to provide 1.21 g (39%) of thiepan-3-one-1,1-dioxide. m.p. 108–110°C; ^{1}H NMR (DMSO-d_6) δ 1.94 (m, 4H), 2.55 (m, 2H), 3.45 (m, 2H), 4.49 (t, 2H, $J = 1.4$ Hz); MS (DCI/NH_3) m/z 180 $(M + NH_4)^+$; Anal. Calcd. for $C_6H_{10}O_3S$: C, 44.43; H, 6.21; S, 19.77. Found: C, 44.49; H, 6.05; S, 19.68.

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Received in the USA August 14, 2003

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