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A NEW METHOD FOR THE CONVERSION OF ENOL PHENYL THIOETHERS TO KETONES

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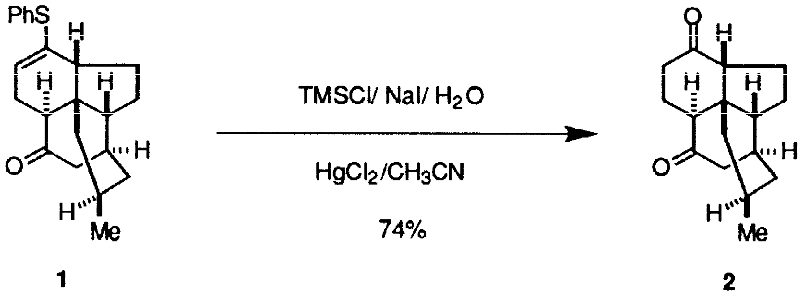
Abstract: Exposure of enol thioethers at ambient temperature to *in situ*-generated hydrogen iodide in acetonitrile containing mercuric chloride gives rise to ketones in yields ranging from 74 - 87%.

Over the years, a number of methods have been developed for the hydrolysis of enol thioethers to ketones, in part, because hydrolysis, often times, proves to be problematic. A case in point is the conversion of tetracyclic keto enol thioether **1** into diketone **2**. For example, exposure of **1** to standard hydrolysis conditions [$HgCl_2$, CH_3CN:H_2O (3 : 1), reflux][1] gave rise to only recovered starting material. Equally disappointing was the use of titanium tetrachloride[2] in either moist methylene chloride at ambient temperature or moist acetic acid at 80 °C which afforded, in both cases, low yields (10 - 15%) of the desired tetracyclic diketone **2**. We detail below a new method for the hydrolysis of enol phenyl thioethers (cf. **1** → **2**) which employs *in situ*-generation of hydrogen iodide in acetonitrile containing mercuric chloride.



Attempts to hydrolyze vinyl sulfide **1** with anhydrous hydrochloric acid in benzene followed by treatment with mercuric chloride in aqueous tetrahydrofuran[3] provided only trace amounts of diketone **2**. In contrast, use of an *in situ*-generated hydrogen iodide protocol[4] [addition of water to chlorotrimethylsilane/sodium iodide] in the presence of mercuric chloride in acetonitrile gave rise to **2**. Thus, exposure (2h, ambient temperature) of enol phenyl thioether **1**[5] in acetonitrile to excess hydrogen iodide [generated from 3.0 equiv of sodium iodide, 3.0 equiv of chlorotrimethylsilane and 3.0 equiv of water) in the presence of 2.0 equiv of mercuric chloride provided, in 74% isolated yield, crystalline diketone **2**,[8] mp 95.5 - 96.5 °C.

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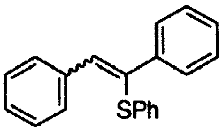
In order to examine the scope of this method for the hydrolysis of enol phenyl thioethers to ketones, a number of substrates have been examined (Table 1). All reactions were carried out 0.04 M in acetonitrile at ambient temperature for 2h in the presence of 3.0 equiv of chlorotrimethylsilane, 3.0 equiv of sodium iodide, 3.0 equiv of water and 2.0 equiv of mercuric chloride. Yields ranged from 74 - 87%. The amount of chlorotrimethylsilane, sodium iodide and water required to effect complete hydrolysis appears to be substrate dependent. For example, in the case of substrate **1**, when only 1.5 equiv each of trimethylchlorosilane, sodium iodide and water were employed along with 2.0 equiv of mercuric chloride, the reaction proceeded very slowly. After 2h at ambient temperature, approximately 70% of the starting enol phenyl thioether remained. In contrast, application of these conditions (1.5 equiv TMSCl, 1.5 equiv NaI, 1.5 equiv H_2O and 2.0 equiv of $HgCl_2$; 2h) to the vinyl sulfide derived from 4-*t*-butylcyclohexanone (entry 3) gave rise to a 73% yield of ketone. Water is required for the transformation, however, the amount does not appear to be critical. In the case of the vinyl sulfide derived from 5α-cholestan-3-one (entry 2), when only 1.5 equiv of water was employed in the presence of 3.0 equiv of TMSCl, 3.0 equiv of NaI and 2.0 equiv of $HgCl_2$, an 85% yield of ketone was obtained after 2h. In the absence of added water, the reaction did proceed, however, at a much slower reaction rate.

The method appears to be general with the exception of β-aryl substituted vinyl sulfides. For example, the vinyl sulfide **3**, derived from deoxybenzoin, upon subjection to the general conditions detailed above (ambient temperature, 2h), gave rise to only recovered starting vinyl sulfide. When the reaction was refluxed for 6h, a <10% yield of deoxybenzoin was obtained.



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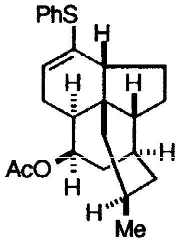
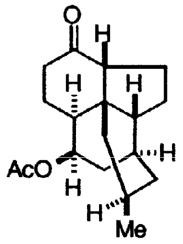
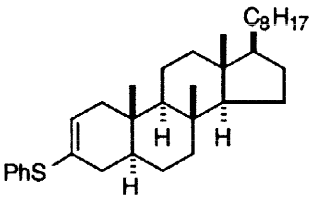
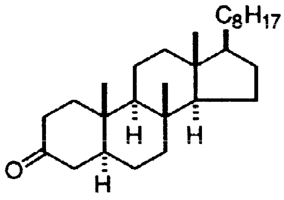
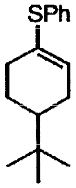
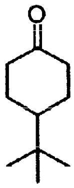
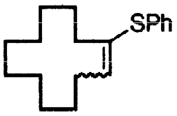
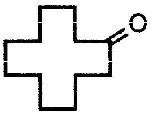
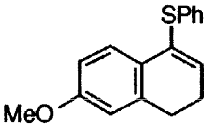
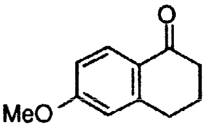
In summary, we have presented a method for the hydroylsis of enol phenyl thioethers which features the *in situ*-generation of hydrogen iodide in moist acetonitrile containing mercuric chloride. This mild, efficient method should be of use to those engaged in complex natural products synthesis.

Typical Experimental Procedure: To a heterogeneous mixture of sodium iodide (90 mg, 0.6 mmol) and mercuric chloride (110 mg, 0.4 mmol) in acetonitrile (2.8 mL), chlorotrimethylsilane (52 μL, 0.6 mmol) was added, followed by the addition of water (10μL, 0.6 mmol). After 5 min at ambient temperature, a solution of 3-phenylthio-Δ^2-cholestene (96 mg, 0.2 mmol) in acetonitrile (1.8 mL)/methylene chloride (0.2 mL) was added. The reaction was allowed to stir at ambient temperature for 2 h. The contents of the reaction flask were filtered through a pad of celite. The filtrate was treated with water (15 mL) and the product was isolated by extraction with ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on silica gel. Elution with hexane:ethyl acetate (18 : 1) afforded 66 mg (87%) of 5α-cholestan-3-one, mp 128 - 129 °C, which was identical in all respects with an authentic sample.

Table 1. Hydrolysis of Enol Phenyl Thioethers to Ketones[a]

Entry	Substrate	Product	Yield (%)[b]
1[c]			75[d]
2[e]			87
3[e]			74
4[e]			82
5[f]			77

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[a] All reactions were carried out 0.04 M in acetonitrile containing 3.0 equiv of TMSCl, 3.0 equiv of NaI, 3.0 equiv of water and 2.0 equiv of $HgCl_2$ at ambient temperature for 2h. [b] Isolated yields. [c] Prepared as described in reference 7. [d] For the ^1H and ^{13}C NMR specrta of the product, see reference 9. [e] The substrate prepared from the corresponding ketone and benzenethiol in the presence of montmorillonite KSF (reference 10). [f] Substrate prepared from 6-methoxy-1-tetralone and benzenethiol in the presence of titanium tetrachloride (reference 11).

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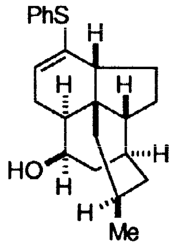
5. Prepared by oxidation of the known alcohol **i**^{6} employing the procedure of Mukaiyama^7 [1.2 equiv of *t*-butoxymagnesium bromide in tetrahydrofuran (10 min) followed by the addition of 1.2 equiv of 1,1'-(azodicarbonyl)dipiperidine in tetrahydrofuran (4h); 98% yield].



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6. Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998,** *120*, 5128.
7. Narasaki, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977,** *50*, 2773.
8. Tetracyclic diketone **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (dd, 1H, J = 5.7, 15.6 Hz), 2.36-2.50 (m, 4H), 2.24-2.36 (m, 3H), 2.02-2.23 (m, 2H), 1.90-2.01 (m, 3H), 1.67-1.90(m, 3H), 1.53 (m, 1H), 1.15-1.28(m, 1H), 0.82 (d, 3H, J = 6.3 Hz), 0.81 (t, 1H, J = 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 211.5, 60.8, 52.5, 49.4, 46.7, 42.7, 42.3, 42.3, 37.3, 34.3, 29.7, 26.6, 24.9, 22.4, 19.8.
9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (t, 1H, J = 6.0 Hz), 2.60 (m, 1H), 2.51 (ddd, 1H, J = 7.6, 10.8, 16.0 Hz), 2.40 (dddd, 1H, J = 1.2, 2.4, 5.6, 16.0 Hz), 2.11-2.28 (m, 3H), 1.81-2.10 (m, 5H), 2.06 (s, 3H), 1.62-1.79 (m, 5H), 1.54 (t, 1H, J = 9.2 Hz), 1.18 (td, 1H, J = 4.8, 12.8 Hz), 0.89 (d, 3H, J = 6.4 Hz), 0.75 (t, 1H, J = 12.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 170.5, 68.3, 63.2, 49.8, 45.9, 42.1, 41.9, 38.4, 35.0, 30.5, 29.6, 26.8, 24.6, 23.9, 23.3, 23.1, 21.5.
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