



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

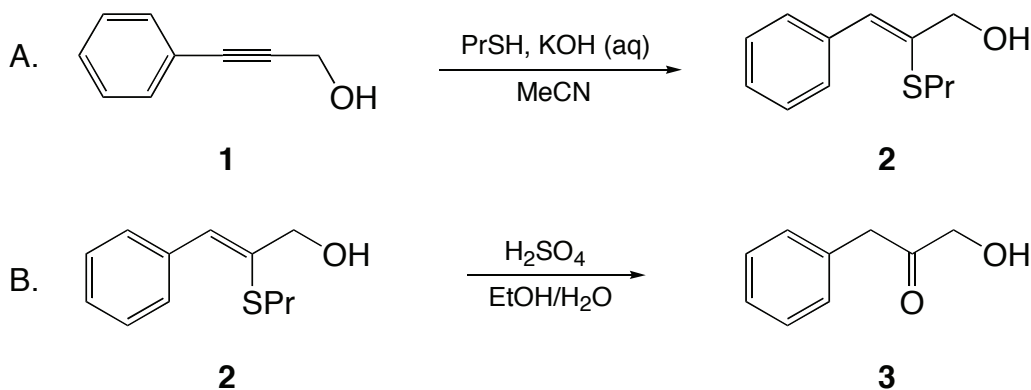
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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1-HYDROXY-3-PHENYL-2-PROPANONE**[2-Propanone, 1-hydroxy-3-phenyl-]**

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Checked by Günter Seidel and Alois Fürstner.

1. Procedure

Caution: The procedures should be carried out in a well-ventilated hood because of the extreme stench of the mercaptan products. All glassware used in the procedures should be rinsed with bleach solution prior to removal from the fume hood.

A. 3-Phenyl-2-(propylthio)-2-propen-1-ol (2). A 250-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, thermocouple probe and nitrogen inlet, is charged with acetonitrile (150 mL), 3-phenyl-2-propyn-1-ol (19.8 g, 0.15 mol), 30 wt% KOH (2.84 g, 15.2 mmol) and 1-propanethiol (14.0 mL, 0.16 mol) (Note 1). The reaction mixture is heated to 60 °C with a heating mantle and stirred for 6 h (Note 2). After cooling to room temperature, the bulk of the solvent is removed under reduced pressure. The resulting yellow oil is taken up in 100 mL of *tert*-butyl methyl ether (TBME) and filtered through 50 g of silica gel (Note 3). The silica gel plug is washed with 300 mL of TBME. The filtrates are combined and concentrated under reduced pressure to give 30.83 g (99%) of 3-phenyl-2-(propylthio)-2-propen-1-ol as a pale yellow oil which can be used without further purification (Note 4).

B. 1-Hydroxy-3-phenyl-2-propanone (3). A 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, thermocouple probe,

rubber septum and nitrogen inlet and outlet that leads to a scrubber containing bleach, is charged with 3-phenyl-2-(propylthio)-2-propen-1-ol (30.1 g, 0.14 mol), 150 mL of ethanol and 150 mL of 1M sulfuric acid. The suspension, which becomes a homogeneous yellow solution, is heated at 65 °C with a heating mantle for 4 h with vigorous stirring and a nitrogen sweep (Notes 5 and 6).

After cooling to room temperature, the reaction mixture is transferred to a 1-L separatory funnel with the aid of 50 mL of water and washed with 250 mL of hexanes, which is discarded (Note 7). After adding 150 mL of brine to the aqueous phase, the product is extracted with ethyl acetate (3 × 250 mL). The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated under reduced pressure (Note 8).

The residue is dissolved in 40 mL of ethyl acetate and filtered through a pad of Celite into a 500-mL round-bottomed flask. With stirring, 240 mL of *n*-heptane is added over 20 min to the ethyl acetate solution via a pressure-equalizing addition funnel. During the addition, the product begins to crystallize as a white solid. The volume of the mixture is reduced by distillation at reduced pressure (20 °C, 10-20 mm) to about 150 mL. The mixture is then cooled to -5 °C and aged for 1 h. The solids are collected via vacuum filtration, washed with heptane (100 mL), and dried under vacuum at room temperature to afford 1-hydroxy-3-phenyl-2-propanone (18.9 g, 87% yield) as white crystals (Note 9).

2. Notes

1. 3-Phenyl-2-propyn-1-ol was purchased from Lancaster Synthesis Ltd. and used as received. 1-Propanethiol was purchased from Aldrich Chemical Company, Inc., and used as received.

2. The reaction progress can be monitored by GC analysis (HP-1701, 15 m × 0.53 mm capillary column, 1.00 μm film thickness, 100 °C increase at 15°/min to 250 °C); the retention time was 4.6 min for the alkynol (**1**) and 7.9 min for the vinyl sulfide (**2**).

3. Silica gel is added to a 300 mL fritted glass funnel and pre-washed with TBME under vacuum, discarding the filtrate. The reaction mixture is poured onto the pad and filtered under vacuum, followed by the TBME washes. An orange layer of by-products remains at the top of the silica gel.

4. The crude product typically contains 2-3% of a by-product resulting from addition to the 3-position of the alkynol, 2-3% of the E-addition product, and residual propanethiol. Spectral data for **2** are as follows: IR cm^{-1} : 3358, 2962, 2930, 2871, 1598, 1491, 1445, 1378, 1291, 1237, 1098, 1078, 1009, 753, 694. ^1H NMR (400 MHz, CDCl_3) δ : 0.96 (t, 3H, $J = 7.3$), 1.60 (m, 2H), 2.76 (t, 2H, $J = 7.3$), 4.37 (s, 2H), 6.83 (s, 1H), 7.2-7.4 (m, 3H), 7.63 (d, 2H, $J = 7.6$); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.4, 23.4, 33.4, 67.0, 127.4, 128.1, 129.5, 129.9, 135.6, 136.3. The checkers obtained **2** in 95% yield. The checkers noted that compound **2** may eventually isomerize to 3-phenyl-2-(propylthio)propanal when kept in CDCl_3 which was not rigorously dried prior to use.

5. A moderate nitrogen purge is necessary to remove the propanethiol, which is formed in the reaction. Care should be taken to treat any distillate collected in the trap with bleach.

6. The reaction rate will depend on the stirring and nitrogen purge rates. The reaction should be monitored for completion (>98% conversion) by GC using the method described in (Note 2); the retention time for hydroxyketone **3** is 4.9 min.

7. The hexanes wash removes thiol-containing by-products and should be treated with bleach prior to disposal.

8. The concentration is done at 20-25 $^{\circ}\text{C}$ at the lowest possible pressure. The hydroxyketone (**3**) is reactive and all product-containing solutions should be maintained below 25 $^{\circ}\text{C}$ during the work up.

9. The physical properties of **3** are as follows: mp 47-48 $^{\circ}\text{C}$; IR (KBr) cm^{-1} : 3378, 1721, 1496, 1454, 1402, 1291, 1076, 1043, 755, 701; ^1H NMR (400 MHz, CDCl_3) δ : 2.94 (s, 1H), 3.74 (s, 2H), 4.30 (s, 2H), 7.2-7.4 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ : 45.9, 67.7, 127.6, 129.0, 129.4, 132.8, 207.3. Anal. Calcd for $\text{C}_9\text{H}_{10}\text{O}_2$: C, 71.98; H, 6.71. Found: C, 71.79; H, 6.70. The checkers obtained material having mp 45-46 $^{\circ}\text{C}$ in 83% yield.

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

Hydroxyketones are versatile intermediates in the synthesis of pharmaceutical intermediates and heterocyclic molecules.² α -Aryl hydroxyketones have been prepared by reaction of aryl aldehydes with 1,4-dioxane followed by reduction with lithium aluminum hydride (LAH)³ and by the selective LAH reduction of α -silyloxy α,β -unsaturated esters.⁴ Wissner⁵ has shown that treatment of acid chlorides with tris(trimethylsilyloxy)ethylene affords alkyl and aryl hydroxymethyl ketones. 1-Hydroxy-3-phenyl-2-propanone (**3**) has been generated by the osmium-catalyzed oxidation of phenylpropene⁶ and by the palladium-catalyzed rearrangement of phenyl epoxy alcohol⁷ both in 62% yield.

The present method is superior in that it requires neither oxidation nor reduction and does not use expensive and toxic heavy metal catalysts. The two step process offers mild conditions and high yields. Recovery of the thiol is possible by using fractional distillation during the hydrolysis, making the process efficient on large scale. The procedure is general for a variety of α -aryl hydroxyketones.⁸

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

1-Hydroxy-3-phenyl-2-propanone: 2-Propanone, 1-hydroxy-3-phenyl- (8, 9); (4982-08-5)

3-Phenyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-phenyl- (8, 9); (1504-58-1)

Propanethiol (9); (79869-58-2)