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Preparation of Cyclopropyl *p*-Hydroxyphenyl Ketone and Its Precursor 3-Chloropropyl *p*-Hydroxyphenyl Ketone

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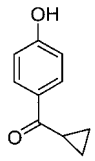
Abstract:

3-Hydroxypropyl *p*-hydroxyphenyl ketone (7) is selectively prepared in 96% yield by the Friedel−Crafts reaction of anisole, 4-chlorobutyryl chloride (5) and aluminum chloride in chlorobenzene at 100 °C, followed by quenching the mixture in aqueous hydrochloride at <40 °C. Heating of the quenched aqueous mixture to 100 °C converts hydroxyl compound 7 cleanly to 3-chloropropyl *p*-hydroxyphenyl ketone (2) in 95−99% yield. Compounds 2 and 7 are interchangeable. Heating chloride 2 with aluminum chloride produces alcohol 7; whereas heating 7 in aqueous hydrochloric acid gives 2 exclusively. The chloride 2 is easily converted to cyclopropyl *p*-hydroxyphenyl ketone (1) at 0 °C using 6 equiv of aqueous sodium hydroxide or 2 equiv of potassium *tert*-butoxide in 92 and 96% yields, respectively.

Various substituted alkoxyphenyl alkyl ketone and cyclopropyl ketones are known to possess a number of biological activities.[1] A key building block to these alkoxyphenyl ketones and one of our recent projects is cyclopropyl *p*-hydroxyphenyl ketone (**1**).



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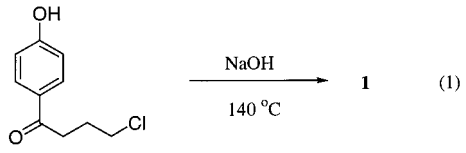
The only known preparations for compound **1** involved refluxing 3-chloropropyl *p*-hydroxyphenyl ketone (**2**) with excess sodium hydroxide[1] (eq 1) or demethylating cyclo-



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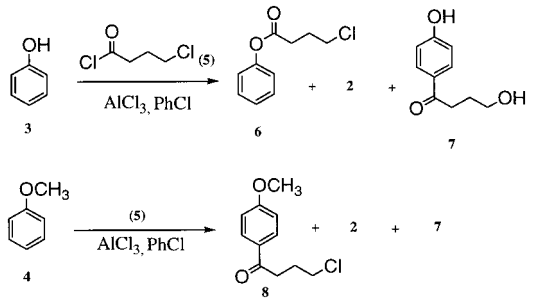
propyl *p*-methoxyphenyl ketone.[2] Either procedure required harsh conditions, giving compound **1** in only poor to moderate yields. Compound **2** by itself has been an important building block for the preparation of anti-microbial compounds[3] and anti-amoebic heterocycles.[4] However, the literature procedures[3] for the synthesis for precursor **2** gave incomplete conversion and mixture of products.

Scheme 1



We now report a selective, high-yielding synthesis for compound **2** and its quantitative conversion to cyclopropyl ketone **1** under very mild conditions.

Preparation of 3-Chloropropyl *p*-Hydroxyphenyl Ketone (2). Compound **2** had been prepared in the literature by the Friedel−Crafts acylation of phenol (**3**) or anisole (**4**) with 4-chlorobutyryl chloride (**5**). However, when we treated phenol (**3**) or anisole (**4**) with 4-chlorobutyryl chloride (**5**) according to the literature procedures, a mixture of compounds was obtained. (Scheme 1) Intermediates such as phenyl ester (**6**) or *p*-methoxyphenyl ketone (**8**) were never completely consumed unless the Friedel−Crafts reactions were carried out at 100 °C or above. We also noticed that the chloride **2** was contaminated by the 3-hydroxypropyl *p*-hydroxyphenyl ketone (**7**). Compound **2** was never isolated cleanly from the reported procedures. Conditions that favor the consumption of the intermediate **6** or **8** also convert chloride **2** to **7**. Table 1 shows the trend of these reactions under various conditions.

In fact, the only product which could be cleanly isolated was alcohol **7**, contrary to the literature report.[3] In general, anisole gave a better yield of compound **7** than did phenol. However, both phenol and anisole could be cleanly converted to **7** in 80 and 96% yields, respectively, by heating the starting material with acid chloride **5** in chlorobenzene to 100 °C for 1−3 h followed by cooling and subsequent quenching with water or dilute hydrochloric acid. Attempts to transform alcohol **7** to chloride **2** using oxalyl chloride or thionyl chloride, alone or in the presence of DMF, gave incomplete reaction. The product was also contaminated with unidentified colored impurities. However, we found that heating alcohol **7** with aqueous hydrochloric acid to 100 °C

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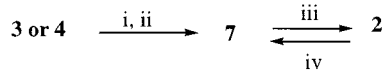
Table 1. **Distribution of Friedel−Crafts acylation products as a function of temperature**

entry	starting material	conditions	**6** or **8**, %[a]	**2**, %[a]	**7**, %[a]
1	**3**	rt, 14 days	3.1	62.4	34.5
		100 °C, 3 h	0	3.0	97.0
2	**3**	40 °C, 39 h	32.6	58.5	8.9
3	**4**	rt, 14 days	51.3	24.8	23.9
		80 °C, 1 h	26.6	9.6	63.8
		100 °C, 3 h	0	5.8	94.2
4	**4**	rt, 16h	57.4	41.0	1.6
		40 °C, 14 h	43.3	31.9	24.8
		100 °C, 1 h	2.1	6.4	91.5
5	**6**	rt, 19h	93.6	6.4	0
		40 °C, 20 h	68.1	23.1	8.8
		60 °C, 24 h	7.8	28.0	64.2
		100 °C, 1 h	0.5	4.6	94.8

[a] HPLC area % adjusted on the solvent-free base.

Scheme 2[a]



[a] i. **5**, $AlCl_3$, PhCl, 100 °C, 1−3 h; ii. H_2O, HCl, <40 °C; iii. H_2O, HCl, 100 °C; iv. $AlCl_3$, PhCl, 100 °C, 1−3 h.

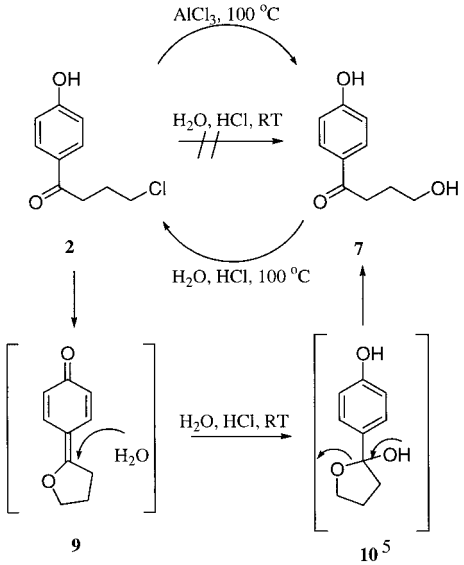
gave chloride **2** exclusively. Thus, reaction of **3** or **4** with **5** can produce either **2** or **7** simply by changing the work-up conditions. The overall transformation is shown in Scheme 2. If the Friedel−Crafts reaction mixture was quenched into water/HCl at low temperature, alcohol **7** was formed exclusively. When this quenched mixture was directly heated back up to 100 °C prior to the isolation, then chloride **2** was produced cleanly.

To demonstrate that **2** was the precursor to **7**, compound **2** was heated to 100 °C with aluminum chloride in chlorobenzene for 2 h followed by aqueous hydrochloric acid quench at rt. Again, compound **7** was isolated in 82.7% yield. Stirring **2** in aqueous HCl for 2 days at rt led to no formation of alcohol **7**. Thus, chloride **2** is the intermediate leading to alcohol **7** and is stable during the acidic work-up.

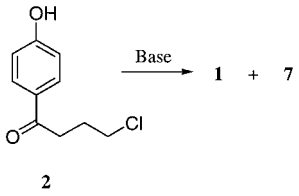
The interconversion of **2** and **7** can be rationalized by the proposed mechanism in Scheme 3. Under the Lewis acid-catalyzed conditions, the initially formed chloride **2** undergoes an intramolecular cyclization to give *p*-quinone methide intermediate **9**. Intermediate **9**, in contact with aqueous HCl, is hydrolyzed to hemiketal **10** which eventually leads to ring-opened product **7** after work-up. Attempts to trap intermediate **9** with thiophenol or 2,3-dimethylbutadiene had failed to produce tractable materials.

Preparation of Cyclopropyl *p*-Hydroxyphenyl Ketone (1). With a good synthesis for chloride **2** in hand, we set out to examine the preparation of cyclopropyl ketone **1**. All literature precedents for cyclopropyl phenyl ketones bearing various substituents on the phenyl rings called for refluxing **2** or its analogues with aqueous sodium hydroxide (eq 1). The yields were about 70%. We found this procedure gave a major impurity identified as 3-hydroxypropyl *p*-hydroxyphenyl ketone (**7**) possibly via intermediate **9**. Further study showed that the level of compound **7** was a function of temperature and the equivalents of sodium hydroxide. Higher

Scheme 3



temperature or less sodium hydroxide favors the formation of impurity **7**. (Table 2) However, the impurity could be significantly reduced by performing the reaction at 0 °C with at least 6 equiv of sodium hydroxide. When potassium *tert*-butoxide was used as the base, reaction could be done at 0 °C in THF, MTBE, or DME, producing cyclopropyl ketone **1** in 95−98% yield. Impurity **7** was not formed under such conditions. Another advantage of using potassium *tert*-butoxide was that the product solution thus produced (a potassium phenolate) could be further elaborated without isolation. In a typical reaction, chloride **2** was added as solid to a stirred aqueous sodium hydroxide (6 equiv) solution or potassium *tert*-butoxide (2 equiv) in THF at 0−5 °C. After completion the product solution was added to a stirred dilute phosphoric acid at 5−10 °C to precipitate the product.



In conclusion, 3-chloropropyl *p*-hydroxyphenyl ketone (**2**) and 3-hydroxypropyl *p*-hydroxyphenyl ketone (**7**) have been selectively prepared in high yields by acylation of anisole with 4-chlorobutyryl chloride (**5**), followed by demethylation, simply by selecting the appropriate work-up conditions. Compounds **2** and **7** can be interconverted either by heating with aluminum chloride or aqueous HCl. Chloride **2** can be converted to cyclopropyl ketone **1** in >95% under very mild conditions in either aqueous sodium hydroxide or potassium *tert*-butoxide in various organic solvents.

Experimental Section

General Methods. All commercial compounds and deuterated solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) or Acros Organics and used without further purification. Melting points were taken with MEL-TEMP II from Mel-Temp Laboratory Devices Inc. without correction.

Table 2. **Cyclization of 3-chloropropyl *p*-hydroxyphenyl ketone (2)**

entry[a,b]	base (equiv)	solvent	PTC added	addn. temp (°C)	rxn. temp, time	ratio of **7**/**1**	isolated yield of **1** (%)
1	NaOH (2)	H_2O	Bu_4NBr	22−29	rt, 3 h	78.0	*d*
2	NaOH (4)	H_2O	-	21−24	rt, 1.5 h	20.3	62.5
3	NaOH (6)	H_2O	-	23−25	rt, 1 h	12.8	*d*
4	NaOH (6.4)	H_2O	Bu_4NBr	22−26	rt, 5 h	7.9	*d*
5	NaOH (10)	H_2O	-	23−32	rt, 3 h	5.6	44.1
6	NaOH (6)	H_2O	-	0−5	rt, 3.5 h	4.2	92.0
7	NaOH (6)	H_2O	-	−5 to 0	rt, 5 h	6.4	91.8
8	KO*t*-Bu (2.2)	*c*	-	−5 to 0	rt, 30 min	0	95.8

[a] Entries 1−5: Adding sodium hydroxide solution to chloride **2**. [b] Entries 6−8: Adding chloride **2** to sodium hydroxide solution. [c] (Entry 8) Solvents successfully used: THF, DME, MTBE [d] Product not isolated.

3-Hydroxypropyl *p*-Hydroxyphenyl Ketone (7). A slurry of aluminum chloride (29.6 g, 0.22 mol) in 15 mL of chlorobenzene was cooled to 10 °C, and anisole (**4**, 20.0 g, 0.185 mol) was added at 10−20 °C, forming a thicker paste. 4-Chlorobutyrylchloride (**5,** 26.1 g, 0.185 mol) was then added dropwise, keeping the temperature at 10−15 °C. Gas evolution was seen during the addition of the acid chloride. At the end of the addition, the clear solution was stirred at room temperature for 16 h and then heated to 100 °C for 1 h to complete the reaction.

The thick, dark-brown mixture was poured into a stirred mixture of 150 mL of water and 50 mL of concentrated HCl at 0−20 °C. The resulting slurry was stirred at room temperature for 2 h. The tan-colored precipitate was filtered, washed with water until the filtrate was neutral, and then vacuum-dried at 45 °C to give the crude product (27.0 g) as brown solid. The crude product could be crystallized from heptane/ethyl acetate (5:2) with 80% recovery. Mp 143−144 °C. Lit. mp[5] 144 °C. The crude product had the same purity as the crystallized material (>96% pure by HPLC) and can be used directly. MS: $(M + H)^+ = 181$. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.85 (d), 6.83 (d), 4.5 (broad s), 3.4 (t), 2.95 (t), 1.75 (m).

3-Chloropropyl *p*-Hydroxyphenyl Ketone (2). A slurry of aluminum chloride (320.6 g, 2.4 mol) in 200 mL of chlorobenzene was cooled to −10 °C. Anisole (**4,** 200 g, 1.85 mol) was added at −10 to 10 °C. 4-Chlorobutyrylchloride (**5,** 286.9 g, 2.04 mol) was added dropwise at 0−10 °C. The reddish mixture was stirred at room temperature for 1 h and then heated to 100 °C for 3 h to complete the reaction.

A solution of 1 L of water and 1.5 L of concentrated HCl was cooled to 5 °C, and the reaction mixture was added, forming a slurry. The slurry was heated to 100 °C for ∼9 h until the reaction was complete and then stirred at rt overnight. The brown precipitate was filtered, rinsed with 1 L each of water, 5% $NaHCO_3$, and water. The wet cake was vacuum-dried at 50 °C to give the crude product (350.7 g, 95.5%). HPLC purity 92.9%. The crude product was crystallized from heptane/2-propanol (4:1) with 61% recovery. Mp 114−116 °C. Lit. mp[3] 114−115 °C. MS: $(M + H)^+ = 199$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.93 (d), 6.9 (d), 3.7 (t), 3.15 (t), 2.2 (m).

Conversion of Compound 2 to 7. To a mixture of aluminum chloride (1.75 g, 13.1 mmol) in 30 mL of chlorobenzene was added compound **2** (2.0 g, 10 mmol). The mixture was heated to 100 °C for 5 h. The mixture was cooled to rt and added to 50 mL of water with vigorous stirring. The precipitate was filtered and washed with water until the filtrate was neutral. The product was dried in vacuo in an oven at 45 °C to give compound **7** as a brownish solid. Yield was 1.5 g (82.7%).

Cyclopropyl *p*-Hydroxyphenyl Ketone (1) A solution of 50% NaOH (24.2 g, 0.3 mol) in 25 mL of water was cooled to 7 °C. Solid 3-chloropropyl *p*-hydroxyphenyl ketone (**2**, 10 g, 50 mmol) was added at 7−8 °C. Water (50 mL) was added, and the clear, light-brown solution was stirred at room temperature for 6 h.

A solution of phosphoric acid (34.3 g, 86%, 0.3 mol) in 30 mL of water was cooled to 5 °C. The reaction mixture was added to the acid at 5−10 °C. Precipitate formed immediately. NaOH (5.3 g, 50%) was added to adjust the pH to 5. After 1 h stirring at rt, the precipitate was filtered, washed with 150 mL water, and vacuum-dried at 30 °C to give the crude product (7.9 g) as a light-brown solid. The crude material can be dissolved in 20 mL of 2-propanol and precipitated with 65 mL of water to improve the purity. Mp 107−109.5 °C. Lit. mp[4] 108 °C. MS: $(M + H)^+ = 163$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.95 (d), 6.9 (m), 2.65 (m), 1.25 (m), 1.15 (m).

Cyclopropyl *p*-Hydroxyphenyl Ketone (1): Nonaqueous System. A solution of potassium *tert*-butoxide (49.7 g, 0.443 mol) in 100 mL of THF was cooled to −5 °C. To this was added the solution of the chloride **2** (40 g, 0.20 mol) in 120 mL of THF at −5 to 0 °C. The mixture was stirred at 0 °C for 30 min and added to a stirred solution of phosphoric acid (30.2 g, 85%, 0.26 mol) in 200 mL of water at −5 to 0 °C. The mixture was warmed to rt and stirred for 2 h. The mixture was extracted twice with ethyl acetate (200 mL + 100 mL). The combined organic layers were washed with 2 × 160 mL of water. The aqueous layers were combined and re-extracted with 150 mL of ethyl acetate. The ethyl acetate extracts were combined, concentrated to oil, and azeotropically dried with ethyl acetate to give a brown oil (36.48 g) which solidified on standing. The crude product was purified by column chromatography (silica gel, 1:1 ethyl acetate: hexane) to give 31.0 g of pure ketone **1**.

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