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# *Communications to the Editor*

## One-Pot Preparation of 7-Hydroxyquinoline

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**Abstract:**

**An efficient one-pot procedure for the four-step preparation of 7-hydroxyquinoline (1) from 3-*N*-tosylaminophenol (4) in 60% isolated yield, that reduces the risk of exposure to acrolein (2), is described.**

### Introduction

7-Hydroxyquinoline (**1**) is a key intermediate in a number of pharmaceutically interesting compounds including Vinblastine.[1] However, it is only commercially available in gram quantities. Its synthesis (Scheme 1) has been reported in the literature[1,2] and requires a large excess of very highly toxic[3] acrolein (**2**), isolation and purification through chromatography of the intermediate *N*-tosyl 7-hydroxyhydroquinoline (**3**), to remove the 5-regioisomer **3a**, or final purification of **1** through salt formation[1,2] with nitric acid.

For our purposes we required an efficient process whereby the amount of acrolein (**2**) was optimized and exposure to **2** minimized. Our study of the conversion (Scheme 3) of 3-*N*-tosylaminophenol (**4**) to **1** by $^1$H NMR and HPLC led to the development of an efficient one-pot process, whereby **1** is directly isolated from the reaction mixture in sufficient quality to be used without further purification. We now report our results.

### Results and Discussion

Initially, to overcome the use of **2** we investigated the use of 3-halopropylaldehyde diethyl acetals (**6** and **7**, X = Cl, I) (Scheme 2) as safer alternatives.

The reaction between **4** with either **6** or **7** under basic conditions, in various solvents, orders of additions, and reaction temperatures afforded a wasteful mixture of **4**, **8**, and the *N*,*O*-alkylated[4] compound **9**. Formation of quinolines via classical Skraup chemistry[5] was not a viable option owing to poor yields and poor regiochemistry. Consequently, we investigated the reaction between **2** and **4**, with the intent of optimizing the amount of **2** required and developing a process with no distillations or isolations of intermediates to reduce the risk of exposure to **2**. The study of the reaction between **2** and **4**, by $^1$H NMR led to the optimization of the amount **2** required, as well as the selection of reaction solvent (Scheme 3). The data[6] showed that after 2 h in ethanol at −5 °C with 5 mol equiv of **2**, 95% conversion to the ethyl acetal **8** (R = Et) rather than to the aldehyde **5** had occurred. In contrast in methanol at − 5 °C, 5 mol equiv of **2** afforded only 65% conversion with product being the aldehyde **5** rather than the methyl acetal **10** (R = Me). Presumably, in methanol the addition to acrolein is less efficient because the major product, aldehyde **5**, may undergo a retroaddition reaction, via the enol **11**, back to starting materials **2** and **4** (Scheme 3). In ethanol, however, **5** is readily converted to the stable acetal **8**, and consequently, the reaction is driven to completion. Further experiments showed the reaction to be more efficient in ethanol than methanol, and in ethanol at −5 °C a minimum of 1.5 mol equiv of **2** were required to achieve 95% conversion after 6 h.

Therefore, the optimum conditions for the addition step were chosen as 1.5 mol equiv of **2** in ethanol at −5 °C for

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(1) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama. T. *Pure. Appl. Chem*. **2003**, *75*, 29−38.

(2) Tokuyama, H.; Sato, M.; Ueda, T.; Fukuyama, T. *Heterocycles* **2001**, *54*, 105. Tokuyama, H.; Fukuyama, T. U.S. Patent Application Publication US 2004/0034217 A1.

(3) The Occupational Safety and Health Administration (OSHA) legal airborne permissible exposure limit (PEL) is 0.1 ppm averaged over an 8-h work shift, and 0.3 ppm not to be exceeded during any 15-min work period (National Institute for Occupational Safety and Health). For a summary of the hazards associated with acrolein, see: *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Urben, P. G., Ed.; Butterworth-Heinemann: Oxford, 1999; Vol. 1, pp 406−407.

(4) Compound **9**: $^1$H NMR (400 MHz, $(CD_3)_2SO$) $\delta$ 1.00 (6H, t, $J$ = 7.2 Hz), $\delta$ 1.06 (6H, t, $J$ = 7.2 Hz), 1.54 (2H, q, $J$ = 6.8 Hz), 1.89 (2H, q, $J$ = 6.8 Hz), 3.32 (3H, s), 3.25−3.55 (10 H, m) 3.83 (2H, t, $J$ = 6.8 Hz), 4.46 (1H, t, $J$ = 5.2 Hz), 4.62 (1H, t, $J$ = 5.2 Hz), 6.54 (1H, t, $J$ = 2.0 Hz), 6.58 (1H, dd, $J$ = 1.6, 8.4 Hz), 6.85 (1H, dd, $J$ = 2.43, 8.4 Hz), 7.20 (1H, t, $J$ = 8.0 Hz) 7.33 (2H, d, $J$ = 8.4 Hz), 7.42 (2H, d, $J$ = 8.4 Hz).

(5) Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59.

(6) Compound **3**: $^1$H NMR (400 MHz, $CD_3Cl_3$) $\delta$ 2.35 (3H, s), 4.42 (2H, dd, $J$ = 1.6, 4.0 Hz), 5.45 (1H, dt, $J$ = 4.0, 9.6 Hz), 5.2 (1H, br) 5.95 (1H, dt, $J$ = 1.6, 9.6 Hz) 6.7 (1 H, dd, $J$ = 2.4, 8.4 Hz), 6.8 (1H, d, $J$ = 8.4 Hz), 7.1 (2H, d, $J$ = 8.4 Hz) 7.4 (2H, d, $J$ = 8.4 Hz). Compound **4**: $^1$H NMR (400 MHz, $(CD_3)_2SO$) $\delta$ 2.30 (3H, s), 6.35 (1H, dd, $J$ = 2.0, 8.0 Hz), 6.47 (1H, dd, $J$ = 2.0, 8.0 Hz), 6.53 (1H, t, $J$ = 2.0 Hz), 6.90 (1H, t, $J$ = 8.0 Hz), 7.30 (2H, d, $J$ = 8.4 Hz), 7.60 (2H, d, $J$ = 8.4 Hz), 9.36 (1H, br, NH), 10.03 (1H, br OH). Compound **5**: $^1$H NMR (400 MHz, $CD_3Cl_3$) $\delta$ 2.42 (3H, s), 2.68 (2H, t, $J$ = 7.2 Hz), 3.85 (2H, t, $J$ = 7.2 Hz), 6.46 (1 H, d, $J$ = 8.0 Hz), 6.70 (1H, s), 6.80 (1H, d, $J$ = 8.0 Hz), 7.13 (1 H, t, $J$ = 8.0 Hz), 7.25 (2H, d, $J$ = 8.4 Hz), 7.49 (2H, d, $J$ = 8.4 Hz). Compound **8**: $^1$H NMR (400 MHz, $CD_3Cl_3$) $\delta$ 1.10 (3H, t, $J$ = 7.2 Hz), 1.53 (2H, q, $J$ = 6.8 Hz), 2.35 (3H, s) 3.33 (2H, m), 3.43−3.48 (4H, m), 4.45 (1H, t, $J$ = 5.5 Hz), 6.38 (1H, dd, $J$ = 1.6, 8.4 Hz), 6.45 (1H, t, $J$ = 2.1 Hz), 6.86 (1H, dd, $J$ = 1.6, 8.0 Hz), 7.08 (1H, t, $J$ = 8.0 Hz), 7.34 (2H, d, $J$ = 8.4 Hz), 7.41 (2H, d, t $J$ = 8.4 Hz), 9.53 (1H, br).

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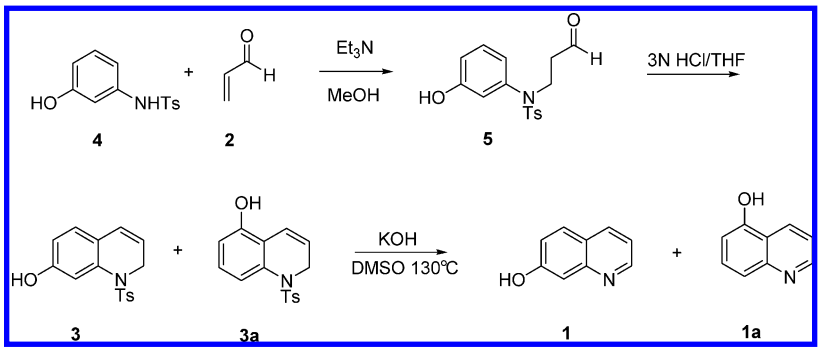
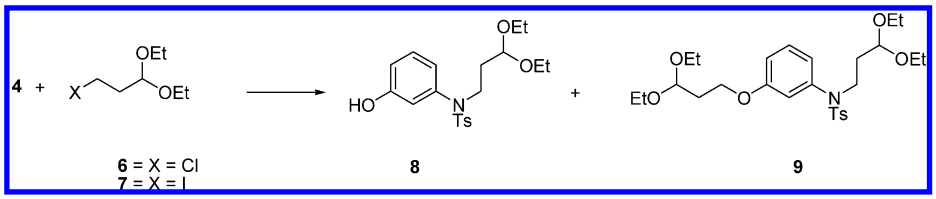
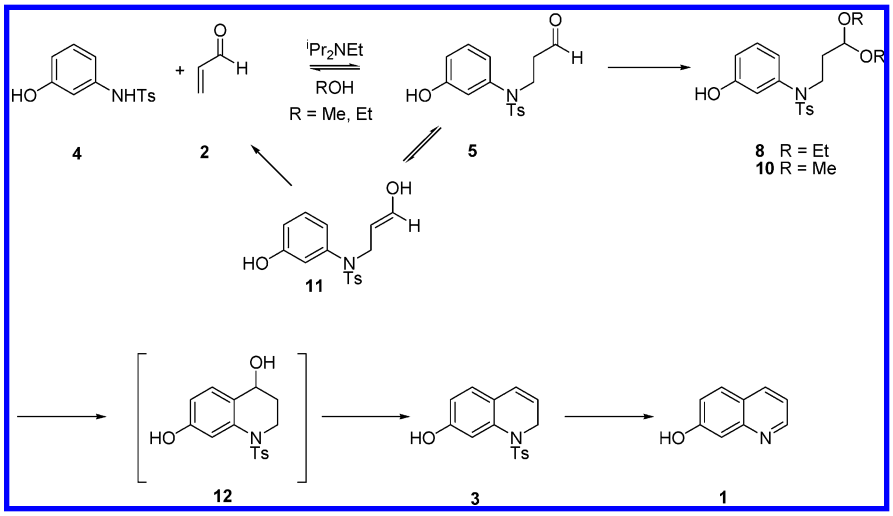
***Scheme 1***




***Scheme 2***




***Scheme 3***




6 h. The treatment of the ethanolic solution of **8** with 5 N HCl resulted in the following sequence of reactions: hydrolysis of **8** to **5**, followed by an intramolecular Friedal Crafts reaction to afford **12** with subsequent elimination of water to yield hydroquinoline **3**. The course of these of events was best suited to analysis by HPLC rather than $^1$H NMR owing to difficulty in interpreting the NMR data due to overlapping signals resulting from a mixture of **3**, **5**, and **12**. HPLC analysis revealed the maximum concentration of **3** was obtained after aging 16 h at ambient temperature followed by heating at 45 °C to drive the conversion of **12** to **3** to completion. Under these conditions **3** was obtained in 70−80% assay yield from **4**. Lower yields were obtained by heating the mixture from the onset at 45 °C, and this was attributed to the instability of the aldehyde **5** at higher temperatures. Cooling the solution of **3** to 0 °C and subsequent cautious addition of excess KOH and heating at reflux for 16 h led to elimination[7] of toluenesulphinic acid to afford **1** in 85−90% assay yield. Adjusting the basic solution[8] to pH 7, by the addition of 6 N HCl, resulted in the precipitation and isolation of **1** in 60% yield from **4**. Under these conditions **1a** is rejected, and the isolated material is typically of sufficient quality (<0.3% 5-regioisomer **1a**) to be used without further purification. However, analytically pure **1** may be obtained by recrystallization from ethanol. The concentration of **2**, in the reaction liquor, at each step of the preparation can be determined[11,12] quantitatively by a HPLC assay for the hydrazone derived from **2** and 2,4-dinitrophenylhydrazine (Table 1). The results show, that at the point of isolation, **2** is present at 4 ppm. In conclusion we have developed an efficient one-pot preparation (Scheme 4) of 7-hydroxyquinoline (**1**) from 3-*N*-tosylaminophenol (**4**) in 60% isolated yield. The risk of

(7) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin 1* **1974**, 2185−2190. Wardani, A.; Lhomme, J. *Tetrahedron Lett.* **1993**, *34*, 6411−6414.

(8) A small volume of toluene is added prior to pH adjustment to solubilize polymeric material that otherwise adheres to the precipitated 7-hydroxyquinoline (**1**).

(9) HPLC assay against commercial material as standard.

(10) 1.7 g of **1** (6%) is lost to the toluene layer.

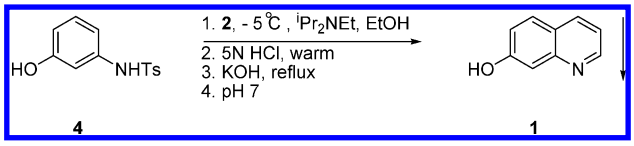
(11) Grosjean, D.; Fung, K. *Anal. Chem.* **1982**, *54*, 1221−1224.

(12) Koivusami, E.; Haatainen, E.; Root, A. *Anal. Chem.* **1999**, *71*, 86−91.

***Table 1.*** **Determination of the concentration of acrolein (2) ($\mu$g g$^{-1}$) in the reaction mixture at key stages**

| reaction stage | acrolein ($\mu$g g$^{-1}$) |
|---|---|
| formation of **5** | 11510 |
| formation of **3** | 138 |
| isolation of **1** | 4 |

***Scheme 4***




exposure to very highly toxic acrolein (**2**) is greatly reduced since no isolation of the intermediates **3** or **5** are required, (Table 1), and **1** is isolated directly by filtration from the reaction mixture at a point where **2** is present at 4 ppm compared with 138 and 11510 ppm for isolation of intermediates **3** and **5**, respectively (Table 1).

## Experimental Section

The HPLC assay for the determination of concentration of intermediates **3**, **8**, and **12** and final purity of **1** was performed with a YMC basic 5.5 $\mu$m (250 mm $\times$ 4.6 mm) column at 25 °C, and compounds were detected at 210 nm. Separation was achieved by employing a gradient elution (60% A for 5 min, then to 20% A over 15 min, and then held at 20% A for a further 5 min) of two mobile phases A and B at a flow rate of 1.5 mL min$^{-1}$. Phase A consisted of 0.1% phosphoric acid in water, and phase B consisted of acetonitrile. For $^1$H NMR analysis reactions were sampled and volatiles evaporated in vacuo; the residues were dissolved in either $(CD_3)_2SO$ or $CDCl_3$ and were run without delay. Conversion was measured as a function of proton integration of **4** against products **5** and/or **8**.

The HPLC assay[11,12] for the determination of acrolein (**2**) concentration was performed on a Waters SymmetryShield RP 18, 3.5 $\mu$m, (150 mm $\times$ 4.6 mm) column at 40 °C, and compounds were detected at 365 nm. Separation was achieved by employing a gradient elution (30% B, 20% C to 65% B and 5% C over 20 min) of three mobile phases A, B, and C at a flow rate of 1.5 mL min$^{-1}$. Phase A, water, phase B, acetonitrile, and phase C, THF. The limit of quantification was established at 0.08 ng, and limit of detection was calculate to be 0.03 ng.

Commercial samples of 7-hydroxyquinoline were obtained from ACROS Organics (Fisher Scientific International Inc.), product number 41882 0010, and 5-hydroxyquinoline was obtained from Aldrich, product number 12,879-1.

***N*-Tosyl-3-aminophenol (4).** To a stirred slurry of 3-aminophenol (252.7 g, 2.29 mol) and pyridine (200 mL, 2.47 mol) in $CH_2Cl_2$ (1250 mL) at −4 °C was added tosyl chloride (473.1 g, 2.43 mol) portionwise over 40 min while maintaining reaction temperature <5 °C. The solution was stirred at 0−5 °C for 1 h and then at ambient temperature for 16 h. Water was added (1000 mL) followed by 12 N HCl (100 mL). The resulting suspension stirred for 1 h, and the solidwas isolated by filtration. The solid was washed on the filter with water (3 $\times$ 200 mL) and then dried to give **4** (556.6 g, 2.11 mol) in 92% yield. $^1$H NMR: (400 MHz, $(CD_3)_2SO$) $\delta$ 2.30 (3H, s), 6.35 (1H, dd, $J$ = 2.0, 8.0 Hz), 6.47 (1H, dd, $J$ = 2.0, 8.0 Hz), 6.53 (1H, t, $J$ = 2.0 Hz), 6.90 (1H, t, $J$ = 8.0 Hz), 7.30 (2H, d, $J$ = 8.4 Hz), 7.60 (2H, d, $J$ = 8.4 Hz), 9.36 (1H, br, NH), 10.03 (1H, br OH). $^{13}$C NMR: (100 MHz, $(CD_3)_2SO$) $\delta$ 158.3, 143.6, 139.4, 137.3, 130.3, 130.1, 127.2, 111.5, 110.8, 107.2, 21.4.

**7-Hydroxyquinoline (1).** To a stirred solution of *N*-tosyl-3-aminophenol (**4**) (100.0 g, 379.9 mmol) and diisopropylethylamine (5.0 mL, 28.8 mmol) in ethanol (500 mL) cooled to −7 °C was added acrolein (**2**) (38 mL, 570.0 mmol) over 1 h, maintaining a batch temperature of −5 to −10 °C. The reaction mixture was aged at −2 to −10 °C for 4 h. A solution of 6 N HCl (128 mL, 768.0 mmol) was added to the reaction mixture over 15 min. The reaction mixture was warmed to 20 °C and stirred for 16 h. The mixture was then heated to 45 °C and stirred for a further 4 h to give **3** as a solution (740 mL) at 124 mg mL$^{-1}$ concentration in 80% assay yield. A portion of this solution (500 mL, **3**, 62.0 g, 205.8 mmol) was then cooled to −6 °C and solid KOH (140.0 g, 2.1750 mol) added over 10 min, while maintaining temperature <25 °C. The mixture was then heated at reflux temperature for 24 h. The mixture was then cooled to 15 °C and toluene[8] (50 mL) added. Water (100 mL) was then added slowly while maintaining quench temperature <15 °C. Once the addition of water was complete, the mixture was cooled to 0 °C and adjusted to pH 7 by the addition of 5 N HCl (~280 mL). The resulting suspension was stirred for 1 h at 0−5 °C and the solid isolated by filtration. The solid was washed on the filter with water (2 $\times$ 50 mL) and then dried in a vacuum oven under reduced pressure at 40 °C to give **1** (25.10 g, 93% by wt[9]) in 60% isolated[10] assay yield from **4**.$^1$H NMR: (400 MHz, $(CD_3)_2SO$) $\delta$ 7.16 (1H, dd, $J$ = 2.0, 8.8 Hz), 7.22 (1H, dd, $J$ = 4.4, 8.8 Hz), 7.27 (1H, s), 7.76 (1H, d, $J$ = 8.8 Hz), 8.13 (1H, d, $J$ = 8.0 Hz), 8.71 (1H, d, 3.6 Hz), 10.25 (1H, br s). $^{13}$C NMR: (100 MHz, $(CD_3)_2SO$) $\delta$ 159.0, 150.9, 150.0, 136.1, 129.8, 122.8, 119.8, 118.9, 110.4.

**Sample Preparation To Determine Amount of (2) after the Formation of (5).** 2,4-Dinitrophenyl hydrazine (500 mg), an aliquot of 1:1 v/v acetonitrile (ACN) and *N*,*N*-dimethylacetamide (DMAC) (10 mL), 0.5 M $H_2SO_4$ (0.5 mL), and an aliquot of the reaction mixture containing (**5**) (1 mL) were added to a 100-mL volumetric flask and diluted to the mark with diluent 1:1 v/v ACN/DMAC. The solution was diluted to 2000$\times$ using the diluent. An aliquot was assayed using the reverse-phase HPLC method described.

**Sample Preparation To Determine Amount of (2) after the Formation of (3).** 2,4-Dinitrophenyl hydrazine (200 mg), an aliquot of 1:1 v/v acetonitrile (ACN) and *N*,*N*-dimethylacetamide (DMAC) (2 mL), 0.5 M $H_2SO_4$ (0.5 mL), and an aliquot of the reaction mixture containing (**3**) (0.5 mL) were added to a 10-mL volumetric flask and diluted to the mark with diluent 1:1 v/v ACN/DMAC. The solution was diluted to 200$\times$ using the diluent. An aliquot was assayed using the reverse-phase HPLC method described.

**Sample Preparation To Determine Amount of (2) after the Formation of (1).** 2,4-Dinitrophenyl hydrazine (200 mg), an aliquot of 1:1 v/v acetonitrile (ACN) and *N*,*N*-dimethylacetamide (DMAC) (2 mL), 0.5 M $H_2SO_4$ (0.5 mL), and an aliquot of the reaction mixture containing (**3**) (0.5 mL) were added to a 10-mL volumetric flask and diluted to the mark with diluent 1:1 v/v ACN/DMAC. An aliquot was assayed using the reverse-phase HPLC method described.

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