to give a continuous stream emanating from the condenser tip (for heat insulation the pressure-equalizing side arm of the addition funnel was wrapped with several layers of paper towel). The Teflon stopcock on the addition funnel was opened only slightly so as to minimize the entry of the hexane vapors from this inlet and yet fully drain all eluted solvent into the still-pot. Once started, the system was allowed to continue until all of the purple $C_{60}$ had collected in the still-pot (20–30 h). The still-pot was then removed and the solvent evaporated[5] to afford ca. 170 mg of pure (HPLC, UV–vis) $C_{60}$ which was separated from the boiling chips by dissolution in $CS_2$ followed by suction filtration and precipitation from the filtrate with pentane. A new 2000-mL two-neck round-bottom flask containing 1.5 L of hexane was then installed and the above process repeated to elute pure $C_{70}$ from the column (70 h). The solvent was evaporated, and 30 mg of pure (HPLC, UV–vis) $C_{70}$ was isolated. So far we have performed about 15 of these separations, all with high reproducibility.

We believe the reason for the success of the separation lies not only in the use of lowest polarity solvents but also in the elevated temperature[10] due to the Soxhlet extraction process. It is possible that our results would not have been nearly as good had we tried the related apparatus of ref 6.

**Acknowledgment.** We thank the National Science Foundation for support through Grants DMR-88-20933, DMR-91-11097, and CHE-89-08323. We also thank Miklos Csuja for the glassware modifications.

**Registry No.** $C_{60}$, 99685-96-8; $C_{70}$, 115383-22-7; C, 7440-44-0; alumina, 1344-28-1.

(10) Pirkle and Welch (Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1991**, *56*, 6973) have found that better separations of $C_{60}/C_{70}$ occur at higher temperature.

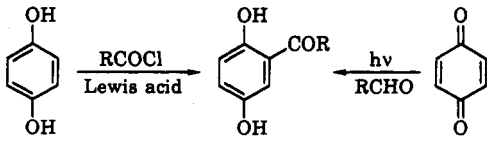
## Quinone Photochemistry. A General Synthesis of Acylhydroquinones

George A. Kraus* and Masayuki Kirihara

*Department of Chemistry, Iowa State University, Ames, Iowa 50011*

*Received September 30, 1991*

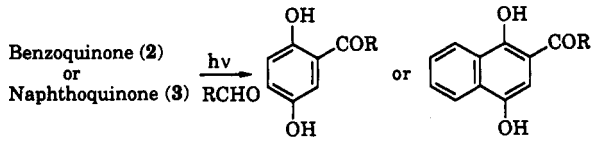
The synthesis of dihydroxy ketones such as **1** is usually accomplished by a sequence involving Friedel–Crafts acylation and hydrolysis.[1] This sequence works well in




**1**

many instances, but imposes certain restrictions on functionality that can be accomodated in both the acyl unit and the aromatic substrate. A direct and potentially general route to these dihydroxy ketones might be the photochemically mediated reaction between a quinone and an aldehyde. Isolated examples of this reaction have been reported.[2,3] In connection with a program designed to explore the biological consequences of modifications on the pyranoquinone skeleton, we have examined this little-used photochemical method for the preparation of our starting materials. Although we had initially used the Friedel–Crafts approach, the poor solubility of some of the intermediates and the modest yields in the acyl-transfer step forced us to examine alternate pathways.

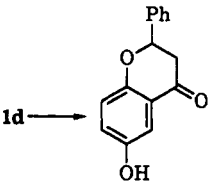
**Table I. Synthesis of 2-Acylhydroquinones**




| entry | | R | % yield | |
|---|---|---|---|---|
| 1 | 2 | Pr | 82 | **1a** |
| 2 | 2 | Ph | 60 | **1b** |
| 3 | 2 | $CH_3CH$=CH | 52 | **1c** |
| 4 | 2 | PhCH=CH | 65 | **1d** |
| 5 | 2 | *o*-$CH_3OC_6H_4$ | 62 | **1e** |
| 6 | 2 | 2-furyl-CH=CH | 32 | **1f** |
| 7 | 3 | Pr | 77 | **4a** |
| 8 | 3 | Ph | 88 | **4b** |
| 9 | 3 | $CH_3CH$=CH | 65 | **4c** |

Benzoquinone (**2**) and 1,4-naphthoquinone (**3**) reacted with a series of aldehydes. The reactions were conducted under an inert atmosphere with a Hanovia lamp with a Pyrex filter. The results are collated in Table I. It is clear from these results that the presence of unsaturation in the aldehyde unit is well tolerated. This reaction has been scaled up to produce multigram quantities of **1a**, **1e** and **4a**.

Interestingly, no intramolecular cyclization occurred in the reactions which produced **1c**, **1d**, **1f**, and **4c**. This observation attests to the mildness of this procedure. Although acylhydroquinone **1d** had been previously prepared,[4] it has always been produced in low yield, the major product being the cyclic ketone **5**. Indeed, hydroquinone




**5**

**1d** has been shown to rapidly cyclize to **5** in the presence of either dilute acid or base. Although hydroquinone **1c** was prepared in 52% yield by the reaction of crotonaldehyde with benzoquinone, **1c** could not be prepared by the $AlCl_3$-mediated rearrangement of the bis-crotonoyl ester of hydroquinone.[5]

This methodology offers a convenient and versatile pathway for the synthesis of acyl hydroquinones. Functional groups such as alkenes are compatible with the mild reaction conditions. This method offers an alternative method for the formation of precursors to highly reactive acylquinones.[6]

(1) Gore, P. H. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; J. Wiley: New York, 1964; Vol. 3, pp 1–382.

(2) Maruyama, K.; Miyagi, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1303.

(3) Klinger, H.; Kolvenbach, W. *Chem. Ber.* **1898**, *31*, 1214. See also: Bruce, J. M.; Creed, D.; Ellis, J. N. *J. Chem. Soc. C.* **1967**, 1486.

(4) Shah, P. R.; Shah, N. M. *Chem. Ber.* **1964**, *97*, 1453.

(5) Bruce, D. B.; Sorrie, A. J. S.; Thomson, R. H. *J. Chem. Soc.* **1953**, 2403.

(6) For a recent preparation of acyl quinones, see: Buchwald, S. L.; King, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 258 and references cited therein.

0022-3263/92/1957-3256$03.00/0 

## Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (SGC). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR and/or NMR, melting point, and TLC comparison with authentic samples.

**Representative Procedure.** Benzoquinone (4.80 g, 44.4 mmol) and freshly distilled butyraldehyde (20 mL, 346.7 mmol) were dissolved in dry benzene (240 mL) and were degassed with nitrogen for 15 min. The solution was irradiated with a high-pressure Hg-vapor lamp with a Pyrex filter for 5 days. The solution was concentrated in vacuo and the residue was purified by SGC using 6:1 H:EA to afford 6.55 g (82% yield) of **1a** as pale yellow crystals.

**1-(2,5-Dihydroxyphenyl)-1-butanone (1a)**: TLC (H:EA = 4:1) $R_f$ = 0.42; mp 94–96 °C (H–benzene) (lit.[7] mp 96 °C).

**(2,5-Dihydroxyphenyl)(phenyl)methanone (1b)**: TLC (H:EA = 4:1) $R_f$ = 0.38; mp 121–123 °C (H–benzene) (lit.[9] mp 122–124 °C).

**1-(2,5-Dihydroxyphenyl)-2-buten-1-one (1c)**: NMR ($CDCl_3$) $\delta$ 1.97 (d, 3 H/2, $J$ = 7 Hz), 2.02 (d, 3 H/2, $J$ = 7 Hz), 6.01–6.07 (m, 1 H), 6.74–6.78 (m, 1 H), 6.87–7.05 (m, 2 H), 7.12–7.26 (m, 1 H), 12.27 (s, 1 H); IR ($CH_2Cl_2$) 1730, 1650, 15.90 $cm^{-1}$; HRMS $m/z$ for $C_{10}H_{10}O_3$ calcd 178.062 99, found 178.062 73; TLC (H:EA = 4:1) $R_f$ = 0.31; mp 114–116 °C ($CHCl_3$–EA).

**3-Phenyl-1-(2,5-dihydroxyphenyl)-2-propen-1-one (1d)**: TLC (H:EA = 4:1) $R_f$ = 0.32; mp 168–170 °C (H–benzene) (lit.[4] mp 170 °C).

**(2,5-Dihydroxyphenyl)(2-methoxyphenyl)methanone (1e)**: NMR ($CDCl_3$) $\delta$ 3.80 (s, 3 H), 6.80 (s, 1 H), 6.92–7.09 (m, 4 H), 7.27–7.30 (m, 1 H) 7.49 (t, 1 H, $J$ = Hz), 11.75 (s, 1 H); IR ($CH_2Cl_2$) 1610 $cm^{-1}$; HRMS $m/z$ for $C_{14}H_{12}O_4$ calcd 244.073 56, found 244.073 12; TLC (H:EA = 4:1) $R_f$ = 0.25; mp 145–148 °C (H–$CHCl_3$).

**3-(2-Furanyl)-1-(2,5-dihydroxyphenyl)-2-propen-1-one (1f)**: NMR ($CDCl_3$) $\delta$ 5.65 (s, 1 H), 6.50–6.51 (m, 2 H), 6.69 (d, 1 H, $J$ = 3 Hz), 6.73–6.78 (m, 2 H), 6.94–6.98 (m, 2 H), 7.53–7.57 (m, 2 H); IR ($CH_2Cl_2$) 1720, 1630 $cm^{-1}$; HRMS $m/z$ for $C_{13}H_{10}O_4$ calcd 230.057 91, calcd 230.057 63; TLC (H:EA = 4:1) $R_F$ = 0.48; MP 134–136 °C ($CHCl_3$–EA).

**(1,4-Dihydroxy-2-naphthyl)-1-butanone (4a)**: TLC (H:EA = 4:1) $R_f$ = 0.50; mp 141–143 °C (H–benzene) (lit.[8] mp 143 °C).

**(1,4-Dihydroxy-2-naphthyl)phenylmethanone (4b)**: NMR ($CDCl_3$) $\delta$ 7.41–7.53 (m, 3 H), 7.56–7.71 (m, 4 H), 8.11 (d, $J$ = 4 Hz, 1 H), 8.50 (d, $J$ = 4 Hz, 1 H), 13.54 (s, 1 H); IR ($CHCl_3$) 1600 $cm^{-1}$; MS CI ($NH_3$) 282 ($M^+ + NH_4$); TLC (H:EA = 4:1) $R_f$ = 0.50; mp 124–126 °C (H–$CHCl_3$).

**(1,4-Dihydroxy-2-naphthyl)-2-buten-1-one (4c)**: NMR ($CDCl_3$) $\delta$ 2.04 (d, 3 H, $J$ = 7 Hz), 7.01 (d, 1 H, $J$ = 6 Hz), 7.08 (s, 1 H), 7.20–7.23 (m, 1 H), 7.57 (t, 1 H, $J$ = 5 Hz), 7.68 (t, 1 H, $J$ = 5 Hz), 8.14 (d, 1 H, $J$ = 5 Hz), 8.47 (d, 1 H, $J$ = 5 Hz), 14.29 (s, 1 H); IR ($CH_2Cl_2$) 1640, 1590 $cm^{-1}$; HRMS $m/z$ for $C_{14}H_{12}O_3$ calcd 228.078 64, found 228.078 54; TLC (H:EA = 4:1) $R_f$ = 0.33; mp 183–186 °C ($CHCl_3$–EA).

**Acknowledgment.** We thank the Hoffmann LaRoche Co. for financial support of this work.

**Registry No.** **1a**, 4693-16-7; **1b**, 2050-37-5; **1c**, 140660-42-0; **1d**, 19312-13-1; **1e**, 140660-43-1; **1f**, 140660-44-2; **2**, 106-51-4; **3**, 130-15-4; **4a**, 72827-02-2; **4b**, 94797-68-9; **4c**, 140660-45-3; $CH_3(CH_2)_2CHO$, 123-72-8; PhCHO, 100-52-7; $CH_3CH{=}CHCHO$, 4170-30-3; $PhCH{=}CHCHO$, 104-55-2; $o$-$CH_3OC_6H_4CHO$, 135-02-4; 3-(2-furyl)-2-propenal, 623-30-3.

**Supplementary Material Available:** Proton NMR data for compounds **1c**, **1e**, **1f**, **4b**, and **4c** (5 pages). Ordering information is given on any current masthead page.

(7) Kurosawa, E. *Nippon Kagaku Zasshi* **1957**, *78*, 312.
(8) Kraus, G. A.; Reynolds, D. L. US Patent 4,965,267.
(9) Herzig, J.; Hoffmann, B. *Chem. Ber.* **1908**, *41*, 143.

## A General and Convenient Synthesis of 3-Aminopyridazines

Jean-Marie Sitamze, Martine Schmitt, and Camille-Georges Wermuth*

*Laboratoire de Pharmacochimie Moléculaire, UPR 421 du C.N.R.S., 5, rue Blaise Pascal, 67000 Strasbourg, France*

*Received October 28, 1991*

During our investigations on psychotropic pyridazine derivatives,[1-4] we needed to prepare 3-aminopyridazines bearing various substituents on the pyridazine ring. Usually, such compounds are prepared by ammonolysis of the corresponding 3-halopyridazines[5] (Scheme I). Depending on the substituents present on the pyridazine ring, this reaction proceeds with extremely variable yields, despite vigorous experimental conditions (autoclave, 100–200 °C, copper catalysts).

The replacement of the halogen atom by other leaving groups was also studied. Thus, Gregory and co-workers prepared 3-amino-6-methylpyridazines by reacting ammonia with the 3-methylthio derivative.[6] After 3 days at 150 °C, the yield was only 18%.

Nucleophilic displacement of 3-alkoxy derivatives is even more difficult.[7] However, 3-mesylated or 3-tosylated pyridazines react with ammonia to give products in yields similar to that observed from 3-halopyridazines.[6,8]

Conversely, the nucleophilic displacement of 3-halopyridazine by means of reagents other than ammonia was also studied (Scheme II). Examples are given by the action of urea on 3-chloro-4-phenyl-6-methylpyridazine[9] and of potassium thiocyanide on 4-bromo-3,5,6-triphenylpyridazine in ethanol, followed by the hydrolysis of the intermediate thiourethane. However, the most convenient method remains the nucleophilic displacement by hydrazine, followed by hydrogenolysis of the initially obtained 3-hydrazinopyridazine.[2,10] This preparation presents the inconvenience of decreasing yields when practiced on samples exceeding 2 g of 3-hydrazinopyridazine.

In the search for a general method giving satisfactory yields and easily applicable on a preparative scale, we became interested in the hydrogenolysis of 3-hydrazinopyridazines by means of nickel–aluminum alloy in alkaline medium which we adapted from Keefer and Lunn.[11] To our knowledge, this reduction procedure, starting from 3-hydrazinopyridazine has never been applied to the production of 3-aminopyridazines. A possible reason may be the observation made by Lunn[12] that in simple pyridazines, nickel–aluminum alloy reduction destroys the

(1) Wermuth, C. G. *Actualités de Chimie Thérapeutique, 12ème série* **1985**, 3–35.
(2) Wermuth, C. G.; Bourguignon, J. J.; Schlewer, G.; Gies, J. P.; Schoenfelder, A.; Melikian, A. *J. Med. Chem.* **1987**, *30*, 239–249.
(3) Wermuth, C. G.; Bourguignon, J. J.; Chambon, J. P.; Worms, P. In *Topics in Pharmaceutical Sciences 1989*; Breimer, D. O., Crommelin, D. J. A., Midha, K. K., Eds.; F.I.P.: The Hague, 1989; pp 325–343.
(4) Wermuth, C. G.; Bizière, K. *Tr. Pharmacol. Sci.* **1986**, *7*, 421–424.
(5) Nakagone, T. In *Pyridazines*; Castle, R. N., Ed.; John Wiley and Sons: New York, 1973; Vol. 28 (Heterocyclic Compounds), pp 463–627.
(6) Gregory, H.; Overend, W. G.; Wiggins, L. F. *J. Chem. Soc.* **1948**, 2199.
(7) Yanai, M.; Kinoshita, T. *Yakugaku Zasshi* **1962**, *82*, 857; *Chem. Abstr.* **1963**, *59*, 1631.
(8) Morren, H. G. Belgian Patent 574,204 (June 24, 1959); *Chem. Abstr.* **1960**, *54*, 5714.
(9) Atkinson, C. M.; Rodway, R. E. *J. Chem. Soc.* **1959**, 6.
(10) Murakani, H.; Castle, R. N. *J. Heterocycl. Chem.* **1967**, *4*, 555.
(11) Keefer, L. K.; Lunn, G. *Chem. Rev.* **1989**, *89*, 459–502.
(12) Lunn, G. *J. Org. Chem.* **1987**, *52*, 1043–1046.

0022-3263/92/1957-3257$03.00/0 