Photoacylation of Electron-Rich Quinones: An Application of the “Photo-Friedel–Crafts Reaction”

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Dedicated to Professor Howard E. Zimmerman on the occasion of his 75th birthday

Abstract: Irradiation of substituted 1,4-benzo- or 1,4-naphthoquinones in the presence of several aldehydes resulted in the formation of acylated hydroquinones in good yields. In the case of 5-acetyloxy naphthoquinone, both regioisomers were formed, but the 2,8-isomer was favored in all cases examined. Even acylated tetrahydroxy naphthalenes became available in good yields by this method.

Key words: acylation, quinones, photochemistry

Naturally occurring quinones are often substituted by electron-rich groups such as alkyl, alkoxy and hydroxy functionalities. Among them are Vitamin K and other important natural products like alkannin, shikonin and others. Since they additionally serve as useful building blocks in organic chemistry, synthetic pathways via Friedel–Crafts acylation, Photo–Fries rearrangement or electrophilic substitution have been described. The photo-reaction between a quinone and an aldehyde represents a useful alternative (Scheme 1), and is therefore often called the “Photo-Friedel–Crafts acylation”.

In this reaction, H-abstraction from an aldehyde by an electronically excited quinone produces acyl radicals, which add to a second ground-state quinone in a free radical chain reaction. An alternative mechanism involving an in-cage recombination of the primarily formed radical pair has been discussed by Maruyama and co-workers, but earlier results by Bruce and co-workers, and more recent studies by us support a free radical mechanism.

We became interested in this photochemical acylation reaction in terms of the solar photochemical synthesis of fine chemicals with sunlight. To find optimal reaction conditions, the photoreaction of 1,4-naphthoquinone with butyraldehyde (Scheme 2) was chosen as a model system for a detailed laboratory study (using an artificial light source). Prolonged irradiation in benzene gave the corresponding acylated hydroquinone in good yield of 79%, whereas in toluene, a nontoxic solvent is needed for solar application, the yield of dropped to 35%. Finally, pure tert-butyl alcohol or its mixture with acetone was found as a suitable alternative, and the photoproduct was isolated in 84% yield (tert-butyl alcohol).

Recently, we have scaled up this reaction to a 500 g scale (1) under solarchemical conditions. Using a sunlight concentrating MAN-Helioman system (Figure 1), irradiation of 1 in the presence of butyraldehyde and in a tert-butyl alcohol–acetone mixture for three days (DLR, Cologne, Germany, August 1996) gave 2 in 90% yield and in high purity.

Figure 1 MAN-Helioman reactor (DLR, Cologne)
For the preparation of potential calixarene precursors, the reaction of 1,4-benzoquinone (3) and 2,4-dimethoxybenzaldehyde (4) was studied giving (2,5-dihydroxyphenyl) (2,4-dimethoxyphenyl)-methanone (5) in 66% yield (Scheme 3).

This reaction was also performed in large scale under solarchemical conditions, and was used as a model system to compare three different sunlight-collecting systems (DLR, Cologne, Germany, September 2000). Beside the MAN-Helioman system (concentration factor CF 15), two simple reactors were used, i.e., the flat reactor (CF 0, Figure 2) and the CPC reactor (CF 3, Figure 3). Interestingly, the last reactor type gave the best results in terms of conversion and product yield.

Figure 2 Flat reactor (DLR, Cologne, Germany); the picture shows Dr. Jürgen Ortner

Figure 3 CPC reactor (DLR, Cologne, Germany)

As an example of a sterically demanding quinone, 2,6-dimethyl-1,4-benzoquinone (6) was selected and irradiated in tert-butyl alcohol with 2,4-dimethoxybenzaldehyde (4) yielding (3,6-dihydroxy-2,4-dimethylphenyl)(2,4-dimethoxyphenyl)-methanone (7) in 60% yield (Scheme 3). Compared to the result obtained with 1,4-benzoquinone (3) itself (66% yield of 5), sterical blocking by the additional methyl groups in 6 plays only a minor role in the photoacetylation step.

Scheme 3

Hydroxy-substituted quinones are often photochemically inert due to their photoinduced enolization. Therefore, this deactivation process needs to be circumvented by protection of the hydroxy group, e.g., in case of 5-hydroxy-1,4-naphthoquinone (juglone) by esterification to its acetate 8. Consequently, irradiation of 8 in benzene and in the presence of several aliphatic aldehydes gave mixtures of the two regioisomeric hydroquinones (9 and 10) in acceptable to good total yields of 59–79% (Scheme 4, Table).

In all cases, the 2,8-regioisomer 9 was formed as the major regioisomer. Compound 9c is of special interest, since it might be used as a precursor for the synthesis of Frenolicin B.

Scheme 4

In order to avoid the formation and thus separation of regioisomers, a symmetrically disubstituted 1,4-naphthoquinone was additionally chosen. Acylation of 5,8-hydroxy-1,4-naphthoquinone (naphthazarin) readily gave compound 11 in almost quantitative yield. Upon irradiation in benzene and in the presence of propionaldehyde, butyraldehyde or 4-methylpentanal (Scheme 5), the corresponding acylated products 12 were obtained in yields between 58% and 60%. Movement of one acetyl group was

Table Isolated Yields of Compounds 9 and 10

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conformed by X-ray analysis. Compound 12c may serve as a useful precursor for the synthesis of alkannan.2

In conclusion, the photochemical Friedel–Crafts acylation is an alternative and useful synthetic route to prepare acylated hydroquinones in acceptable to high yields. 1,4-naphthoquinones carrying free hydroxy groups (i.e., juglone or naphthazarin) are deactivated by competing photooxonolization and therefore, the hydroxy groups have to be protected as acetates prior to irradiation. Since hydroquinones can be easily oxidized to the corresponding quinones by a variety of methods,15 the “Photo-Friedel–Crafts acylation” offers a convenient access to these important key-intermediates.1

All solvents used had p.a. quality or were purified by distillation. Mps were determined using a Büchi B-540 apparatus and are uncorrected. 1D and 2D NMR spectra were recorded on a Bruker AM 250 or DRX 500 spectrometer. UV/Vis spectra were recorded on a Shimadzu UV-2100. For IR spectra measurements, a Perkin–Elmer 841/1600 was used. MS was performed on a Finnigan MAT C 321 or MAT 8230. HRMS (EI, 70eV) on a VG/Visions Autospec X. Irradiations were carried out in a Rayonet photochemical reactor equipped with RPR-4100 lamps (\(\text{F}_{\text{max}} = 419 \pm 10\) nm).

The compounds 8 and 11 were synthesized via esterification of 5-hydroxy-1,4-naphthoquinone (juglone) or 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) as described,16 but the reactions were carried out at r.t. 4-Methylpentanal was synthesized via Grignard reaction as reported in the literature.17

**General Procedure**

A solution of the quinone and the aldehyde in \(\text{t-BuOH}\) or benzene was carefully degassed with Ar and irradiated for 18 h at r.t. The solvent was removed in vacuo, and the products were isolated by HPLC (Column: Merck Si-60, EtOAc–cyclohexane mixtures) or column chromatography (silica gel, EtOAc–cyclohexane mixtures), respectively.

**1-(4,4-Dihydroxy-2-naphthyl)-1-butanone (2)**

Prepared from 1,4-naphthoquinone (1.20 g, 7.50 mmol) and butyraldehyde (4.00 g, 18.00 mmol) in \(\text{t-BuOH}\) (250 mL).

Yield after column chromatography (EtOAc–cyclohexane, 15:85): 1.45 g (84%).

Yellow solid; mp 144–145°C.

1H NMR (CDCl3): \(\delta = 1.02\) (t, 3H, J = 7.5 Hz, CH3CH(=CH)2), 1.79 (tq, 2H, J = 6.9, 7.5 Hz, CH2CH(=CH)2), 2.92 (t, 2H, J = 6.9 Hz, CH2CH(=CH)2), 5.05 (br, 1H, C4-OH), 6.99 (s, 1H, C3-H), 7.55 (dd, 1H, J = 6.9, 8.2 Hz, C6-H/C7-H), 7.66 (dd, 1H, J = 6.9, 8.2 Hz, C7'-H/C6'-H), 8.08 (d, 1H, J = 8.2 Hz, C8-H), 8.44 (d, 1H, J = 8.2 Hz, C5'-H), 13.76 (s, 1H, C1-OH).

13C NMR (acetone-d6): \(\delta = 14.0\) (q, CH3CH(=CH)2), 18.4 (t, CH2CH(=CH)2), 41.0 (t, CH2CH(=CH)2), 105.4 (d, C3-H), 112.9 (s, C-2), 123.0 (d, C8-H/C5-H), 124.7 (d, C5-H/C8-H), 126.7 (s, C8a), 127.0 (s, C7-H), 130.0 (d, C6-H), 130.6 (s, C4a), 145.4 (s, C4-OH), 156.6 (s, C1-OH), 207.2 (s, COCH3).

**2,5-Dihydroxyphenyl(2,4-dimethoxyphenyl)-methanone (5)**

Prepared from 1,4-benzoquinone (175 mg, 1.59 mmol) and 2,4-dimethoxybenzaldehyde 1.32 g (7.96 mmol) in \(\text{t-BuOH}\) (36 mL).

Yield (EtOAc–cyclohexane, 30:70): 288 mg (66%).

Yellow solid; mp 159°C.

IR (KBr): \(\nu = 3312, 1639, 1612, 1577, 1480\) cm\(^{-1}\).

1H NMR (CDCl3): \(\delta = 3.74\) (s, 3H, C4-OCH3), 3.84 (s, 3H, C2-OCH3), 4.89 (s, 1H, CH3), 6.41 (d, 1H, J = 9.1 Hz, CH2), 6.52 (d, 1H, J = 3.1 Hz, C6-H), 6.88 (d, 1H, J = 8.8 Hz, CH2), 6.90 (dd, 1H, J = 3.1, 9.1 Hz, CH, C4a), 7.22 (d, 1H, J = 8.8 Hz, CH), 11.73 (s, 1H, C2-OH).

13C NMR (CDCl3): \(\delta = 45.6\) (q, COCH3), 55.7 (q, OCH3), 98.9 (d, C3-H), 104.5 (d, C5-H), 118.3 (d, C6'-H/C7'-H), 118.8 (s, C3'-H/C6'-H), 120.2 (s, C1'/C1'), 120.4 (s, C1'/C1'), 124.7 (d, C4'-H), 130.9 (d, C6-H), 147.2 (s, C5'-OCH3), 157.0 (s, C2'-OHN), 158.5 (s, C2-OCH3), 163.1 (s, C4-OCH3), 200.8 (s, CO).

HRMS: m/z calcld for C16H13O5C: 274.0841. Found: 274.0835.

**7,4'-Dihydroxy-2,4-dimethylphenyl(2,4-dimethoxyphenyl)-methanone (7)**

Prepared from 2,6-dimethyl-1,4-benzoquinone (160 mg, 1.59 mmol) and 2,4-dimethoxybenzaldehyde (800 mg, 4.82 mmol) in \(\text{t-BuOH}\) (36 mL).

Yield (EtOAc–cyclohexane, 30:70): 214 mg (60%).

Yellow solid; mp 141–142°C.

IR (KBr): \(\nu = 3313, 1639, 1612, 1577, 1480\) cm\(^{-1}\).

1H NMR (acetone-d6): \(\delta = 1.99\) (s, 3H, CH3), 2.27 (s, 3H, CH3), 3.75 (s, 3H, OCH3), 3.91 (s, 3H, OCH3), 6.62 (m, 3H, C3-H, C5-H, C5'-H), 6.80 (s, 1H, C3-OH), 7.49 (d, 1H, J = 8.2 Hz, C6-H), 8.86 (s, 1H, C6'-OH).

13C NMR (acetone-d6): \(\delta = 14.2\) (q, C2'-CH3), 17.1 (q, C4'-CH3), 55.9 (q, OCH3), 56.1 (q, OCH3), 99.4 (d, C3-H), 106.0 (d, C5-H), 116.2 (d, C5'-H), 124.1, 127.1, 129.7, 131.9 (s, 133.7 (d, C6-H), 146.8 (s, C5'-OCH3), 150.1 (s, C6-OH), 161.4 (s, C2-OCH3), 165.2 (s, C4-OCH3), 197.2 (s, CO).

MS (Cl): m/z (%) = 303 (M+ 4).
7-Propionyl-5,8-dihydroxy-1-naphthyl Acetate (9b) and 6-Propionyl-5,8-dihydroxy-1-naphthyl Acetate (10b)

Prepared from 5,8-dioxo-5,8-dihydroxy-1-naphthyl acetate (200 mg, 0.93 mmol) and butyraldehyde (880 mg, 12.2 mmol) in benzene (60 mL).

9c Yield (EtOAc–cyclohexane, 30:70): 111 mg (42%).
Yellow solid; mp 166–167°C.
UV/Vis (EtOH): λ (c) = 325 (32850), 268 (30500), 325 (7700), 405 (12000) nm.
IR (KBr): ν = 3291 (br), 1725, 1635, 1605 cm⁻¹.
1H NMR (CDCl₃): δ = 0.99 (t, 3H, CH₂CH₃), 1.68 (tq, 2H, J = 7.2, 7.4 Hz, CH₂CH₂), 2.48 (t, 2H, J = 7.2 Hz, CH₂CH₃), 2.63 (s, CH₃COO), 6.15 (s, 1H, C5-OH), 6.43 (s, 1H, C6-H), 7.10 (dd, 1H, J = 1.3, 7.4 Hz, C2-H), 7.52 (dd, 1H, J = 7.4, 8.4 Hz, C3-H), 7.68 (dd, 1H, J = 1.3, 8.4 Hz, C4-H), 14.15 (s, 1H, C8-OH).
13C NMR (CDCl₃): δ = 138.8 (q, CH₂CH₃), 17.6 (t, CH₃), 21.5 (q, CH₃COO), 40.5 (q, CH₂CH₂CH₃), 105.9 (d, C6-H), 112.7 (s, C7), 118.6 (s, C8a), 120.1 (d, C2-H), 121.0 (d, C4-H), 128.9 (d, C3-H), 131.7 (s, C8a), 143.3 (s, C5), 148.3 (s, C1), 155.9 (s, C8), 172.7 (s, CH₃COO), 206.4 (s, H₂C₃CH₃).

HRMS: m/z (%) = 288 (M⁺, 20), 246 (100), 203 (68).
MS (Cl): m/z (%) = 289 (M⁺ + 1, 100), 247 (27).

10c Yield (EtOAc–cyclohexane, 30:70): 91 mg (34%).
Yellow solid; mp 163°C.
UV/Vis (EtOH): λ (c) = 258 (33300), 317 (52000), 388 (6700) nm.
IR (KBr): ν = 3559, 3492, 3150 (br), 1747, 1603 cm⁻¹.
1H NMR (CDCl₃): δ = 1.02 (t, 3H, J = 7.4 Hz, CH₂CH₃), 1.78 (tq, 2H, J = 7.3, 7.4 Hz, CH₂CH₃), 2.37 (s, 3H, CH₃COO), 2.93 (t, 2H, J = 7.3 Hz, CH₂CH₃), 6.87 (dd, 1H, J = 1.1, 7.6 Hz, C2-H), 7.12 (br, 1H, C5-OH), 7.28 (dd, 1H, J = 1.6, 8.4 Hz, C3-H), 7.78 (s, 1H, C7-H), 8.01 (dd, 1H, J = 1.1, 8.4 Hz, C4-H), 13.97 (s, 1H, C8-OH).
13C NMR (CDCl₃): δ = 138.9 (q, CH₂CH₃), 17.8 (t, CH₃), 21.5 (q, CH₃COO), 40.5 (q, CH₂CH₂CH₃), 111.6 (s, C6), 115.9 (d, C2-H/C7-H), 115.9 (d, C7-H/C2-H), 117.1 (d, C4-H), 120.3 (s, C8a), 127.1 (d, C3-H), 128.3 (s, C8a), 137.2 (s, C1), 151.5 (s, C8), 160.3 (s, C5), 170.0 (s, CH₃COO), 205.9 (s, H₂C₃CH₃).

HRMS: m/z (%) = 288 (M⁺, 17), 246 (100), 228 (20), 213 (19), 203 (25).
MS (Cl): m/z (%) = 289 (M⁺ + 1, 100), 247 (19).
HRMS: m/z calc for C₁₃H₁₉O₆: 288.0997. Found: 288.0997.

5-(Acetoxyl)-4,8-dihydroxy-3-propionyl-1-naphthyl Acetate (12a)
Prepared from 4-acetoxyl-5,8-dioxo-5,8-dihydroxy-1-naphthyl acetate (220 mg, 0.80 mmol) and propionaldehyde (650 mg, 11.2 mmol) in benzene (84 mL).

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Yield (EtOAc-cyclohexane, 40:60): 160 mg (60%).

Dark yellow solid; mp 159–160°C.

IR (KBr): ν = 3433, 1766, 1629 cm⁻¹.

1H NMR (CDCl₃): δ = 1.25 (t, 3H, J = 7.3 Hz, CH₂CH₃), 3.02 (q, 2H, CH₂CH₂CH₃), 2.37 (3H, H₃CCOOCS), 2.39 (3H, H₃CCOOOC1), 6.92 (d, 1H, J = 8.3 Hz, C6-H), 6.97 (d, 1H, J = 8.3 Hz, C6-H), 7.24 (s, 1H, C8-OH), 7.35 (s, 1H, C2-H), 14.54 (s, 1H, C4-OH).

13C NMR (CDCl₃): δ = 8.2 (q, CH₃CH₂), 21.1 (q, H₃CCOOCS), 21.3 (q, H₃CCOOOC1), 115.8 (d, C7-H), 117.9 (d, C2-H), 120.8 (s, C8a), 121.5 (s, C8a), 121.5 (s, C3), 121.6 (d, C6-H), 137.0 (s, C8-OH), 142.1 (s, C5), 149.8 (s, C1), 160.1 (s, C4-OH), 169.0 (s, H₃CCOOCS), 171.0 (s, H₃CCOOCS), 206.4 (s, H₂CC₃CO).

MS (El): m/z (%) = 374 (M⁺ + H₂CCO, 3), 346 (M⁺, 10), 262 (100).

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References

(10) The results from the solarchemical experiments will be published independently.
(13) Reaction a has been described in the literature using acetaldehyde itself as the solvent: the ratio of 9a and 10a was only determined by NMR spectroscopy of their mixture: Bruce, J. M.; Dawes, K. J. Chem. Soc. C 1970, 645.