

GREEN SYNTHETIC APPROACHES TO FUROYLNAPHTHOHYDROQUINONE AND JUGLONE

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ABSTRACT

The synthesis of two valuable precursors of biological active compounds named 2-(furan-2-yl)-1,4-dihydroxynaphthoquinone **2** and 5-hydroxy-1,4-naphthoquinone (**4**, juglone) *via* solar photo-induced reactions from 1,4-naphthoquinone **1** and 1,5-dihydroxynaphthalene **3** in green solvent media is reported. When *t*-butyl alcohol and the binary *t*-ButOH/DMK and ternary *i*-PrOAc/DMK/MEK solvent mixtures were used, acylhydroquinone **2** was isolated in yields of 80, 83 and 77%, respectively. The sensitized photooxygenation of **3** “on water” and in water containing sodium dodecyl sulfate produce juglone **4** in 81 and 39% yields respectively.

Keywords: Solar light; Photoacylation; Photooxygenation; Green chemistry

INTRODUCTION

Photochemical reactions carried out with sunlight are particularly interesting in the context of green chemistry due to substrate activation often occurs without additional reagents, which diminishes formation of by products, and the renewable nature of the energy source.¹⁻⁴ Over the last few decades, the growing demand for environmentally friendly technologies has attracted rising attention in synthetic organic photochemistry.^{5,6} Solar photoacylation of 1,4-naphthoquinone **1** with furfural to give acylhydroquinone **2** and sensitized photooxygenation of 1,5-dihydroxynaphthalene (1,5-DHN) **3** that provides 5-hydroxy-1,4-naphthoquinone (**4**, juglone) are two representative examples of solar light-mediated synthesis in the field of quinoid compounds (Figure 1). Our continuous interest on quinone chemistry together the usefulness of acylhydroquinone **2** and juglone **4** as precursors of biological active compounds led us to study greener access to these compounds.

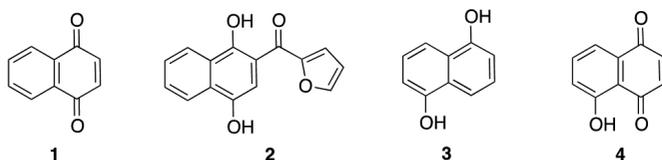


Figure 1. Structure of precursors **1-3** and photoproducts **2-4**.

Herein we wish to report results on the synthesis of acylhydroquinone **2** by photoacylation of 1,4-naphthoquinone **1** with furfural by using solar irradiation in different green solvent media. Greener synthetic approaches to prepare juglone **4** by sensitized photooxygenation of 1,5-dihydroxynaphthalene **3** in water media are also described.

EXPERIMENTAL

General

All reagents and solvents were commercially available reagent grade. Melting points were determined on a Stuart Scientific SMP3 apparatus and are uncorrected. The ¹H-NMR spectrum was recorded on Bruker AM-400 instrument in CDCl₃ + DMSO-*d*₆. The ¹³C-NMR spectrum was obtained at 100 MHz in CDCl₃ + DMSO-*d*₆. Chemical shifts are reported in δ ppm downfield from TMS, and *J*-values are given in Hertz. The mass spectrum was recorded on a Thermo Finnigan spectrometer, model MAT 95XP. Silica gel Merck 60 (70–230 mesh) was used for preparative column chromatography and TLC aluminum foil 60F₂₅₄ for analytical TLC. The solar irradiation experiments were performed in the *Estación Experimental de Canchones, Facultad de Recursos Naturales Renovables, Universidad Arturo Prat* in Iquique/Chile, located in the Atacama Desert.

Chemistry

Photoacylation of 1,4-naphthoquinone **1 with furfural in different solvent media.**

General procedure: A solution of 1,4-naphthoquinone **1** (1 mmol), furfural (7.5 mmol) and the required “preferred Pfizer solvent” (10 mL) into a Pyrex tube was gently bubbled with nitrogen for 2 min. The tube was sealed with a septum and then irradiated with sunlight for five days (total illumination time: 30 h; 800–1150 Watts/m²; November–March). The solvent(s) was removed under reduced pressure and the residue was chromatographed on silica gel (3:1 petroleum ether/ethyl acetate).

(1,4-Dihydroxynaphthalen-2-yl)(furan-2-yl)methanone **2**: orange solid mp, 188.5–189°C ¹H RMN (400 MHz, DMSO-*d*₆ + CDCl₃): δ 13.61 (s, 1H, 1-OH), 9.13 (s, 1H, 4-OH), 8.34 (d, 1H, *J* = 7.8 Hz, 8- or 5-H), 8.12 (d, 1H, *J* = 7.8 Hz, 5- or 8-H), 7.50 (m, 5H, 6-, 7-H and furyl), 6.60 (s, 1H, 3-H). ¹³C NMR (100 MHz, DMSO-*d*₆ + CDCl₃): δ 189.7, 156.3, 144.4, 142.2, 133.5, 132.7, 129.3, 128.8, 127.3, 125.6, 125.3, 123.6, 121.8, 111.3, 105.6. HRMS (APCI): [M+H]⁺ calcd for C₁₅H₁₀O₄: 254.05791; found: 254.05889.

Photooxygenation of 1,5-dihydroxynaphthalene **3** in different solvent media.

General procedure: A solution of 1,5-dihydroxynaphthalene (**3**; 200 mg, 1.25 mmol), rose bengal (20 mg) and the required solvent (150 mL) into a round bottom flask was irradiated by Light Emitting Diode lamps (LED: InGaN, 0.768 W, 42.24 lm, 530 nm) for 5 h at the same time a gently stream of air is bubbled through the solution. Evaporated solvent(s) was frequently refilled. Work up followed by column chromatography over silica gel (3:1 petroleum ether/ethyl acetate) yield pure juglone **4** (orange solid, mp, 153–154°C; lit.⁷: 151–154°C). To evaluate the conversion of **3** and the yield formation of the product **4**, precursor **3** was recovered by column chromatography in each assay. The identity of juglone **4** was corroborated by comparison of their TLC and NMR’s spectral properties with those of an authentic sample.

RESULTS AND DISCUSSION

The solar-chemical experiments reported in this section were developed in the *Estación Experimental de Canchones, Universidad Arturo Prat*, located at latitude 20°26′43,80” S, 990 m above sea level in Chile’s northern desert, Tarapacá. In order to attain high conversion in short time reaction, the solar experiments were conducted during the period November to March, where the radiation reaches highest annual intensities values in the range 720–1150 watt/m² (Graphic 1).

Photoacylation of 1,4-naphthoquinone **1** with furfural in green solvent media.

In a previous work we reported that the solar-induced photoacylation of 1,4-naphthoquinone **1** with furfural proceeds efficiently in benzene to give acylhydroquinone **2** in 89% yield.⁸ In order to explore greener conditions to prepare **2** from naphthoquinone **1** and furfural by avoiding the use of the toxic solvent benzene, a series of photoacylation experiments were run in environmentally benign solvent media. According to the Pfizer solvent selection guide,^{9,10} the following “preferred” solvent were selected: water, ethyl acetate (EtOAc), isopropyl acetate (*i*-PrOAc), ethanol (EtOH), methanol (MeOH), *tert*-butanol (*t*-ButOH), 1-butanol (1-ButOH), 1-propanol (1-PrOH),

2-propanol (2-PrOH), acetone (DMK) and 2-butanone (MEK). The assays were performed under standard conditions (see experimental) and the samples were exposed to the sunlight for 30 h (5 days).

The results of the assays are summarized in Table 1. The data clearly indicate that the efficiency of the photoacylation of **1** with furfural is strongly dependent upon the nature of the solvent media. Thus, the photoacylation performed in EtOAc; 2-PrOH; MEK; *i*-PrOAc gave the photoproduct **2** in low to moderate yields (28-47%) however, when the photoacylation were carried out in *t*-ButOH compound **2** was isolated in 80% yield. No photoacylation reaction was detected when water, EtOH; MeOH; 1-ButOH; 1-PrOH and DMK were employed as the solvent media.

Graphic 1. Solar radiation on Canchones in the period January 2010 to December 2012.

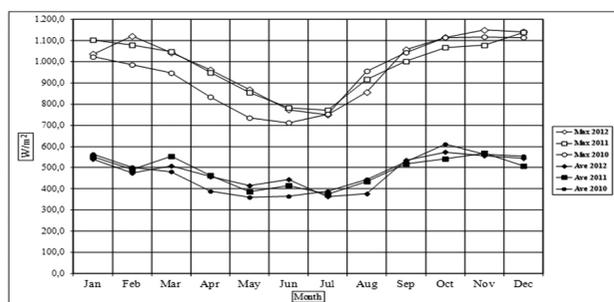
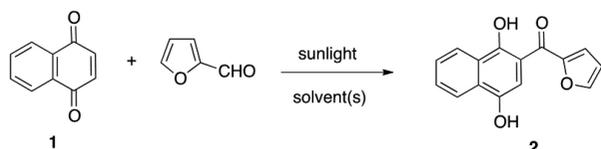


Table 1. Solar photoacylation of quinone **1** with furfural in green solvent media.



Solvent media	Yield (%) ^a	Solvent media	Yield (%) ^a
Benzene	89	<i>t</i> -ButOH	80
Water	nr	1-ButOH	nr
EtOAc	47	1-PrOH	nr
<i>i</i> -PrOAc	28	2-PrOH	45
EtOH	nr	DMK	nr
MeOH	nr	MEK	37
Binary mixture (1:1; v/v proportion)			
EtOAc/2-PrOH	54	<i>i</i> -PrOAc/DMK	28
EtOAc/EtOH ^b	38	DMK/EtOAc ^b	48
EtOAc/MEK	31	<i>t</i> -ButOH/DMK	83
Ternary mixture (1:1:1; v/v/v proportion)			
DMK/2-PrOH/1-ButOH	29	<i>i</i> -PrOAc/DMK/1-ButOH	29
EtOAc/PrOH/ <i>t</i> -ButOH	21	<i>i</i> -PrOAc/DMK/MEK	77
EtOAc/PrOH/EtOH	18	<i>i</i> -PrOAc/EtOAc/ <i>t</i> -BuOH	25
EtOAc/2-PrOH/ <i>t</i> -ButOH	17	<i>i</i> -PrOAc/EtOAc/MEK	41
<i>i</i> -PrOAc/DMK/ <i>t</i> -ButOH	33	<i>i</i> -PrOAc/2-PrOH/ <i>t</i> -BuOH	21

^a) Isolated by column chromatography

^b) 3:1; v/v proportion

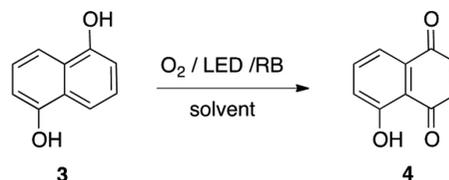
nr: no reaction

It is worth to note that precedents on the photoacylation of naphthoquinone **1** with butyraldehyde in *t*-BuOH and in 3:1 *t*-BuOH/DMK mixture, employing artificial^{11,12} and solar light,¹³ gave the respective acylhydroquinone in 84 and 90% yield, respectively. In the light of these precedents and taking into account the above results on the influence of the solvent media on the photoacylation to produce acylated hydroquinone **2**, we wanted to examine the effect of binary and ternary green solvent mixtures on the photoacylation of quinone **1** with furfural. The result of the photoacylation experiments by using a variety of binary and ternary solvent mixtures are summarized in Table 1. The data of these assays indicate that the photoacylation in binary *t*-ButOH/DMK and ternary *i*-PrOAc/DMK/MEK solvent mixtures produced the acylhydroquinone **2** in 83 and 77%, respectively. Indeed, the use of *t*-ButOH or the binary *t*-ButOH/DMK mixture appears as suitable solvent media to prepare compound **2** by solar photoacylation of **1** with furfural.

Photooxygenation of 1,5-dihydroxynaphthalene **3** in green solvent media.

Then we focused on developing clean preparation of juglone **4** by sensitized photooxygenation of 1,5-dihydroxynaphthalene **3**. There are several reports on the synthesis of juglone **4** by sensitized photooxygenation of **3** in a variety of solvents including green aqueous and ionic liquid solvents.¹⁴⁻¹⁶ We first carried out *in door* experiments on the preparation of juglone **4** from **3** in the “preferred” solvent media: water, EtOAc, *i*-PrOAc, EtOH, MeOH, *t*-BuOH, 1-ButOH, 1-PrOH, 2-PrOH, DMK and MEK. The photooxygenation assays, performed using rose bengal (RB) as sensitizer and LED lamps as radiation source, are summarized in Table 2.

Table 2. Photooxygenation of 1,5-DHN in different solvent media under LED radiation.



Solvent (s)	Conversion (%)	Yield (%) ^a	Solvent (s)	Conversion (%)	Yield (%)
Water	43	55	1-ButOH	43	30
EtOAc	77	17	1-PrOH	49	75
<i>i</i> PrOAc	55	16	2-PrOH	43	83
EtOH	62	64	DMK	46	50
MeOH	27	83	MEK	50	64
<i>t</i> -BuOH	44	35			

^a) Determined on the initial and recovered amounts of precursor **3**

The data of these assays indicate that the photooxygenation of **3** in water; EtOH and MEK solvent media yield product **4** in moderate yields (50-64%). Better yields formation of **4** (75-83%) was achieved in MeOH; 1-PrOH and 2-PrOH solvent media. Based on the conversion of **3** versus yield formation of **4**, the photooxygenation in EtOH is the optimal experimental condition to prepare juglone **4** by LED lamps.

Based on the *in door* photooxygenation experiment of compound **3** “on water” and considering that water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns, the *out door* sensitized photooxygenation of compound **3** on water was examined. The reaction was carried out under standard condition to give juglone **4** in good yield (81%) but low precursor conversion was observed (27%). Interestingly, when the photooxygenation of compound **3** was performed on water, in the presence of 5% mol of sodium dodecyl sulfate to facilitate the transfer of the lipophilic product **4** out of the aqueous medium, high precursor conversion was observed albeit the product **4** was isolated in moderate yield (39%).

CONCLUSION

In summary, we have developed greener access to furoylnaphthohydroquinone **2** and juglone **4** through photoacylation and

photooxygenation procedures induced by solar light. Compound **2** was prepared in 80 and 83% yield by solar photo Friedel Crafts acylation of 1,4-naphthoquinone **1** with furfural in *t*-ButOH and in the binary 1:1 *t*-ButOH/MEK solvent media. The use of the ternary 1:1:1 *i*-PrOAc/DMK/MEK solvent mixture also provides green preparation of compound **2** (77%).

The photooxygenation of 1,5-dihydroxynaphthalene **3** sensitized with Rose Bengal conducted in EtOH; 1-PrOH and 2-PrOH solvent media provides clean and efficient access to juglone **4** (75-83%). The photooxygenation of **3** performed "on water" and in water containing sodium dodecyl sulfate yield juglone **4** in 81 and 39% yield, respectively.

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REFERENCES

1. A. Albini and M. Fagnoni. *Green Chem.*, **6**, 1, (2004).
2. J. Mattay. *Chem. Unserer Zeit*, **36**, 98, (2002).
3. A. Albini, M. Fagnoni and M. Mella. *Pure Appl. Chem.*, **72**, 1321, (2000).
4. A. G. Griesbeck, W. Kramer and M. Oelgemöller. *Green Chem.*, **1**, 205, (1999).
5. P. Tundo, P. Anastas, D. StC. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Poliakoff and W. Tumas. *Pure Appl. Chem.*, **72**, 1207, (2000).
6. P. T. Anastas and J. C. Wagner. *Green Chemistry: Theory and Practice*. Oxford University Press, Oxford, 1998.
7. H. J. Duchstein and G. Wurm, *Arch. Pharm. (Weinheim)*, **317**, 809, (1984).
8. J. Benites, D. Ríos, P. Díaz and J. A. Valderrama. *Tetrahedron Lett.*, **52**, 609, (2011).
9. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak. *Green Chem.*, **10**, 31, (2008).
10. R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons. *Green Chem.*, **13**, 854, (2011).
11. M. Oelgemöller, C. Schiel, J. Mattay and R. Fröhlich, *Eur. J. Org. Chem.*, **15**, 2465, (2002).
12. C. Schiel, M. Oelgemöller and J. Mattay, *Synthesis*, **8**, 1275, (2001).
13. M. Oelgemöller, C. Jung, J. Ortner, J. Mattay, C. Schiel and E. Zimmermann, *The Spectrum*, **18**, 28, (2005).
14. O. Suchard, R. Kane, B. J. Roe, E. Zimmermann, C. Jung, P. A. Waske, J. Mattaya and M. Oelgemöller. *Tetrahedron*, **62**, 1467, (2006).
15. M. Oelgemöller, J. Mattay and H. Görner. *J. Phys. Chem. A*, **115**, 280, (2011).
16. B. Murphy, P. Goodrich, C. Hardacre and M. Oelgemöller. *Green Chem.*, **11**, 1867, (2009).