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Synthesis of Acylated Naphthohydroquinones Through Photo-Friedel–Crafts Acylation and Evaluation of Their Antibiotic Potential

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Abstract: A variety of 1-(1,4-dihydroxynaphtalen-2-yl) ketones was synthesized using the photo-Friedel–Crafts acylation of 1,4-naphthoquinone with aldehydes. Subsequent oxidation using silver oxide readily furnished the corresponding 2-acylated 1,4 naphthoquinones. Notably, these naphthoquinone derivatives underwent spontaneous partial reduction upon storage. The synthesized compounds were subjected to antimicrobial screening. High inhibition effects on *Staphylococcus aureus* were found for the majority of compounds, which makes them interesting for potential future medicinal applications.

Keywords: photoacylation; naphthoquinones; acylated naphthohydroquinones; antibiotic activity

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1. Introduction

Acylated 1,4-naphthohydroquinones and their naphthoquinone equivalents are known for their broad biological activities (Figure 1). Compounds **I** and **IV**, for example, showed antibiotic properties [1–3], while derivatives **II**, **III** and **V** demonstrated cytotoxic activities instead [4–6].

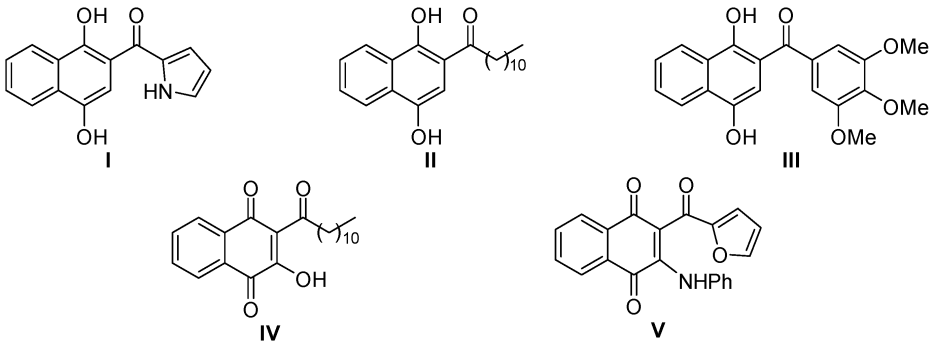


Figure 1. Examples of bioactive acylated naphthoquinones and naphthohydroquinones.

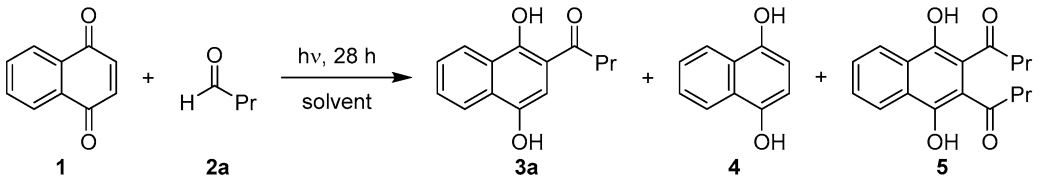
The photochemical acylation or 'photo-Friedel–Crafts acylation' of quinones with aldehydes represents a rapid pathway for the construction of acylated 1,4-naphthohydroquinones [7], although the term 'photo-Friedel–Crafts' reaction has also been suggested for other transformations [8–10]. This versatile photoreaction was initially discovered in 1888, when solutions of the starting materials were exposed to natural sunlight for long periods of time [11]. Since its rediscovery as a simple synthesis procedure by Kraus et al. in 1992 [12],

several improved synthesis protocols have been developed. Friedrich and co-workers found that irradiations of 1,4-naphthoquinone with aliphatic aldehydes with UVB light significantly shortened the reaction time [13]. In 2011, Benites et al. described solar exposure experiments for the heteroacylation of 1,4-quinones [14]. A major improvement was the replacement of benzene with trifluorotoluene (TFT) as a much more sustainable solvent by Mitchell and co-workers [15]. Subsequent oxidation, most commonly using silver (I) oxide, readily yields the corresponding naphthoquinones [16]. The photoacylation of quinones is now routinely used in the discovery of biologically active compounds [3–6,17–21]. The aim of this study was to synthesize libraries of acylated naphthohydroquinones and naphthoquinones and to study their antimicrobial activities.

2. Results and Discussion

2.1. Optimization Studies

Initially, the currently known reaction protocols were further improved in terms of their convenience in producing larger quantities of the desired acylation products. To achieve this, several parameters, i.e., choice of organic solvent, wavelength, glass type and light sources, were examined experimentally. The photoaddition of 1,4-naphthoquinone (**1**) with excess amounts of butyraldehyde (**2a**) was selected as a model system (Scheme 1), as **2a** and the corresponding acylation product **3a** are not prone to Norrish-type follow-up reactions under the chosen experimental conditions [22,23]. Irradiations were carried out in a Rayonet photochemical chamber reactor, reaction progress was monitored by TLC and conversions and compositions were determined by ^{1}H-NMR analysis of the crude products. In line with previous observations [7], no reaction was observed in the dark.



Scheme 1. Photoacylation of 1,4-naphthoquinone with butyraldehyde as a model system for process optimization.

2.1.1. Solvent Optimization

A series of photoreactions of **1** (1 mmol) and **2a** (5 mmol) in different degassed organic solvents (50 mL) was conducted with UVB light (300 ± 25 nm) in a Pyrex Schlenk flask (Table 1). In acetone, exhaustive irradiation for 28 h was necessary until TLC analysis indicated the near-complete consumption of **1** (entry 1). All subsequent irradiations were thus performed for the same duration. In most cases, the corresponding acylated naphthohydroquinone **3a** was readily obtained in isolated yields of 51–76%.

Table 1. Experimental results of the solvent optimization study (300 ± 25 nm, Pyrex, 28 h).

Entry	Solvent	Conversion (%) [1]	Yield of 3a (%)
1	acetone	95	76 [2]
2	acetonitrile	94	75 [2]
3	trifluorotoluene	100	62 [3]
4	xylenes	64	51
5	*tert*-amyl alcohol	86 (30 [4])	n.d. [5]
6	*tert*-butyl alcohol	87 (4 [4])	67
7	isopropanol	73 (46 [4])	n.d. [5]

[1] Determined by ^{1}H-NMR analysis (±3%). [2] After trituration with cyclohexane. [3] After successive filtrations. [4] Amount of photoreduction product **4** in crude product. [5] Not determined.

The experimental results revealed a dependency of chemoselectivity, i.e., photoacylation to **3a** vs. photoreduction to **4**, on the organic solvent used. The most selective conversions occurred in acetone, acetonitrile and trifluorotoluene (entries 1–3). In contrast, photoreduction of naphthoquinone to **4** was observed in alcoholic solvents (entries 5–7) [24]. In line with observations made by Mitchell et al. [15], the polar photoacylation product **3a** precipitated during irradiation in trifluorotoluene and was collected by successive filtrations. The product **3a**, which strongly absorbs within the UVB range, was thus largely removed from the reaction mixture, hence reducing light-filtering effects, and enabling complete conversion [25]. The photochemical activation mode, i.e., direct excitation vs. photosensitization, also depended on the solvent system, and triplet sensitization was assumed to operate in acetone [26]. A similar sensitization pathway was proposed in the presence of benzophenone [27]. While acetone and acetonitrile produced higher yields, their flammability and toxicity make them less attractive for large-scale syntheses [28].

2.1.2. Wavelength Optimization

Glass has a profound impact on light transmission [29]. To find the optimum wavelength for irradiation, the emission of the light sources and the glass type of the reaction vessel were thus investigated. A range of additional photoacylations involving the **1**/**2a** model system were consequently performed for 28 h in a Pyrex ($\lambda \geq 300$ nm) or quartz ($\lambda \geq 200$ nm) vessel with different UV as well as visible lamps (Table 2). Almost no reaction was observed upon irradiation with visible light in TFT (entry 1), whereas irradiation with UVA light gave complete conversion and an isolated yield for **3a** of 55% (entry 5). Quartz-filtered UVB light in acetone also showed photoreduction to **4** (entry 6). Likewise, irradiations with UVC light in quartz vessels furnished by-products **4** and **5** in both acetone and acetonitrile (entries 7 and 8). Bisacylation products similar to **5** have been occasionally described, but their formation remains largely unclear to this day [7,30].

Table 2. Experimental results of the wavelength optimization study.

Entry	Irradiation Conditions	Solvent	Conversion (%) [1]	Yield of 3a (%)
1	visible light, [2] Pyrex	trifluorotoluene	trace	n.d. [3]
2	visible light, [2] Pyrex	acetone	54	21 [4]
3	419 ± 25 nm, Pyrex	acetone	66	56 [5]
4	350 ± 25 nm, Pyrex	acetone	80	60 [5]
5	350 ± 25 nm, Pyrex	trifluorotoluene	100	55 [6]
6	300 ± 25 nm, Quartz	acetone	74 (22 [7])	50 [4]
7	254 nm, Quartz	acetone	96 (35 [7], 28 [8])	30 [4]
8	254 nm, Quartz	acetonitrile	89 (8 [7], 38 [8])	40 [4]

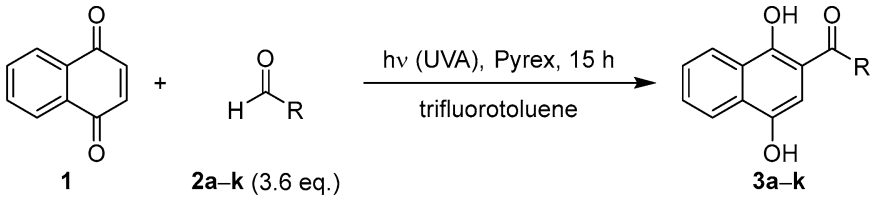
[1] Determined by ^{1}H-NMR analysis (±3%). [2] Cool white fluorescent tubes. [3] Not determined. [4] After column chromatography. [5] After trituration with cyclohexane. [6] After successive filtrations. [7] Amount of photoreduction product **4** in crude product. [8] Amount of bisacylation product **5** in crude product.

Based on these results, the optimal preparative irradiation parameters were TFT as the solvent, UVA light and Pyrex as the reaction vessel material. Under these conditions, selective and complete conversion was achieved, and the precipitated photoproduct could be easily isolated by successive filtration and subsequent drying. Although irradiation with UVB light produced a slightly higher yield of **3a**, it may initiate degradation reactions for longer-chained aliphatic aldehydes or experience strong filtering for aromatic aldehydes or their respective photoacylation products, respectively [31,32].

2.2. Photoacylations

In order to produce adequate amounts of material for subsequent oxidations and screening in a single run, the amount of **1** was increased 7-fold and the irradiation time was shortened to 15 h. To further suppress undesired interferences, the amount of aldehyde was further reduced to 3.6 equivalents. Applying these modified conditions, 1,4-naphthoquinone (7 mmol) was irradiated in the presence of various aldehydes **2a**–**k**

(25 mmol) for 15 h in 140 mL of TFT (Scheme 2 and Table 3). In almost all cases, the desired colored photoacylation products readily precipitated and were isolated by consecutive filtration in yields of 22–57%. The collected amounts were sufficient for further investigations but may be increased upon further optimization. Irradiation with isobutyraldehyde (**2d**) and benzaldehyde (**2h**) gave rather complex mixtures, presumably due to competing photo-oxidations [33], and consequently demanded purification by column chromatography instead (entries 4 and 8). All photoproducts exhibited a characteristic sharp singlet peak between 13 and 14 ppm in their ^{1}H-NMR spectra, representing the newly formed hydroxy group at C-1 locked in an intramolecular hydrogen bond with the acyl-carbonyl group. Analysis of the liquid waste streams revealed the presence of residual photoacylation products **3** and minor by-products, particularly bisacylation products similar to **5**, but no attempts were made to isolate these compounds. Importantly, no degradants from Norrish-type cleavage reactions could be detected for the aliphatic aldehydes and their photoacylation products **3a**–**g**. Photoacylations involving benzaldehydes showed variable yields, which suggests a correlation with the stability of their respective acyl-radical intermediates [34].



Scheme 2. Photoacylation of 1,4-naphthoquinone with various aldehydes.

Table 3. Experimental results of photoacylations of 1,4-naphthoquinone with various aldehydes.

Entry	R	Yield of 3 (%) [1]
1	C_3H_7	53/45 [2] (**a**)
2	CH_3	50 (**b**)
3	C_2H_5	57 (**c**)
4	$CH(CH_3)_2$	45 (**d**) [3]
5	C_4H_9	57/47 [2] (**e**)
6	C_6H_{13}	54/43 [2] (**f**)
7	$C_{11}H_{23}$	57 (**g**)
8	Ph	37 (**h**) [3]
9	*p*-MeC_6H_4	22 (**i**)
10	*p*-FC_6H_4	50 (**j**)
11	*p*-$MeOC_6H_4$	45 (**k**)

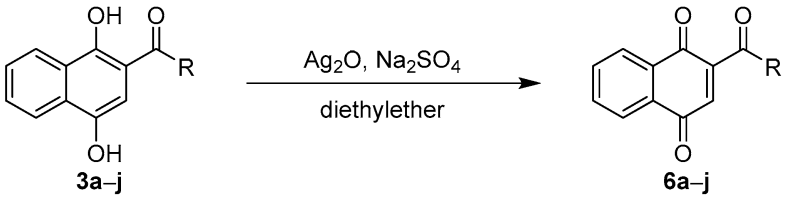
[1] After successive filtration. [2] Solar exposure. [3] After column chromatography.

Selected transformations were furthermore performed in natural sunlight [11,15,35]. Test tubes containing degassed solutions of **1** and aldehydes **2a**, **e** and **f** were illuminated for 4 days under partially sunny conditions and furnished somewhat lower yields to those obtained with artificial UVA light of 43–47%.

2.3. Oxidations

The photoacylation products **3a**–**j** were readily oxidized with freshly prepared silver (I) oxide in diethyl ether and in the presence of sodium sulfate as a drying agent (Scheme 3) [16]. The acylated naphthoquinones **6a**–**j** were obtained as colorful solids in yields of 72–98% (Table 4). The identity of the compounds was confirmed by the absence of the hydroxy-group peaks in their ^{1}H-NMR and the presence of three carbonyl singlet peaks between 180 and 200 ppm in their ^{13}C-NMR spectra. Upon storage, spontaneous partial reduction of the acylated naphthoquinones to their corresponding naphthohydroquinones was noticed in the solid state. All compounds were thus stored in dry amber flasks under nitrogen.

Importantly, these spontaneous reductions pose a significant challenge to the usability of acylated 1,4-naphthoquinone derivatives and must be considered when synthesizing, analyzing or utilizing these compounds.



Scheme 3. Oxidation to acylated naphthoquinones.

Table 4. Experimental results of oxidations of acylated 1,4-naphthoquinones.

Entry	R	Yield of 6 (%)
1	C_3H_7	97 (**a**)
2	CH_3	96 (**b**)
3	C_2H_5	98 (**c**)
4	$CH(CH_3)_2$	72 (**d**)
5	C_4H_9	98 (**e**)
6	C_6H_{13}	98 (**f**)
7	$C_{11}H_{23}$	98 (**g**)
8	Ph	75 (**h**)
9	*p*-MeC_6H_4	95 (**i**)
10	*p*-FC_6H_4	95 (**j**)

Complete reductions were also observed during GC-MS analyses and the same chromatograms and spectra to those of their corresponding photoproducts **3a–j** were recorded. This thermal reduction was likely caused by the presence of water vapor as known from other MS studies of quinones [36].

2.4. Antimicrobial Activity Testing

Due to the known antimicrobial activity of naphthoquinones and their derivatives, all acylated naphthohydroquinones and selected naphthoquinone analogues synthetized were subjected to antibiotic activity screening [37]. The disc diffusion method versus suitable control antibiotics was chosen using the following five bacteria [38,39]: *Staphylococcus aureus* and *Enterococcus faecium* as Gram-positive strains and *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* as Gram-negative strains, respectively. Initial screening was performed with 220 µg doses to identify any hit compounds. All compounds showed strong inhibition of *S. aureus*, which justified further dilution studies (Table 5).

At concentrations of 100 µg and 10 µg, the dodecanoyl derivatives **3g** and **4g** were found inactive (entries 7 and 17). After a further reduction to 5 µg, compounds **3j**, **6a**, **6c** and **6f** also failed to show any activity (entries 10, 12, 14 and 16). For all other bacteria screened, isolated weak to moderate activities were observed for some of the compounds. In particular, the short-chained derivatives **3a**, **3b**, **3e**, **6a** and **6c** also inhibited *E. faecium* and *E. coli*. Only naphthoquinone **6c** additionally inhibited *K. pneumoniae*, while naphthohydroquinones **3c** and **3j** showed moderate activities against *E. faecium* as well. In contrast, none of the substances tested showed any activity against *P. aeruginosa*. These results confirm the potential of acylated naphthohydroquinones, in particular, to inhibit bacterial growth. However, more research needs to be conducted to gain a deeper understanding of their efficacy and suitability as antibiotics.

Table 5. Antimicrobial activity of photoacylation and oxidation products against *S. aureus*.

Entry	Compound	Inhibition (cm) [1]		
		100 µg	10 µg	5 µg
1	**3a**	strong	moderate	moderate
2	**3b**	strong	moderate	weak
3	**3c**	strong	moderate	moderate
4	**3d**	strong	moderate	moderate
5	**3e**	strong	moderate	moderate
6	**3f**	strong	moderate	moderate
7	**3g**	inactive	inactive	inactive
8	**3h**	strong	moderate	moderate
9	**3i**	strong	moderate	moderate
10	**3j**	strong	moderate	inactive
11	**3k**	strong	moderate	moderate
12	**6a**	strong	moderate	inactive
13	**6b**	strong	moderate	weak
14	**6c**	strong	weak	inactive
15	**6e**	strong	moderate	weak
16	**6f**	strong	moderate	inactive
17	**6g**	inactive	inactive	inactive
18	**6i**	moderate	moderate	moderate
19	**6j**	strong	moderate	moderate

[1] In comparison with fosfomycin (200 µg) as control.

3. Materials and Methods

3.1. General Information

All chemicals were purchased from Sigma-Aldrich or Carl Roth and were used as received. Irradiation experiments were carried out in a Rayonet RPR-200 photochemical chamber reactor (Southern New England Ultraviolet Company, Branford, CT, USA) equipped with 16 × 8 W UVA (350 ± 25 nm), UVB (300 ± 25 nm), visible light (cool white, 400–700 nm) or UVC (254 nm) fluorescent or germicidal tubes. Pyrex ($\lambda \geq 300$ nm) or quartz ($\lambda \geq 200$ nm) Schlenk flasks with capacities of 60 and 180 mL were used as reaction vessels. A cold finger was inserted into the flask to maintain the reaction temperature below 25 °C. The reaction mixtures were degassed with N_2 through a sidearm for approx. 5 min before capping the reaction vessel. Photoreactions were monitored by thin-layer chromatography (TLC) or ^{1}H-NMR spectroscopy. Solar exposures were conducted in Pyrex test tubes at Building A of Hochschule Fresenius in Idstein, Germany (50°22′ N, 8°27′ E), in May 2024.

3.2. Photoacylations

3.2.1. General Procedure for Photoacylations with Artificial Light

A solution of 1,4 naphthoquinone (**1**, 7 mmol) and aldehyde (**2a**–**k**, 25 mmol) in 140 mL of trifluorotoluene was prepared in a Pyrex Schlenk flask. The mixture was degassed for 5 min with nitrogen and irradiated for 15 h with UVA light (16 × 8 W Ushio F8T5BL, Tokyo, Japan). Any precipitated photoproduct **3a**–**k** was filtered off and the liquid filtrate was evaporated to dryness. The semisolid to oily residue was sonicate with little cyclohexane until a precipitation was formed. After resting, the solid was filtered off. The trituration process was repeated until no more precipitate was obtained. The combined solid material was dried in vacuum. When no precipitation was formed, the crude reaction mixture was evaporated to dryness and the oily residues were subjected to column chromatography using a mixture of cyclohexane and ethyl acetate (4:1) as mobile phase.

3.2.2. General Procedure for Solar Photoacylations in Sunlight

A solution of 1,4 naphthoquinone (**1**, 6 mmol) and aldehyde (**2a**, **e** or **f**, 25 mmol) in 120 mL of trifluorotoluene was spread over 6 Pyrex test tubes. Each solution was degassed with nitrogen for 5 min, the tubes were capped and exposed to sunlight for 4 days. In

all three cases, precipitates formed during illumination. The products were isolated by successive filtration as described above.

All photoacylation products **3a**–**k** are known and their spectroscopic details match previously described data [12,13,15,40,41]. Characteristic spectroscopic details of **3a**–**k** are compiled in the Supplementary Materials.

3.3. Oxidations

3.3.1. Synthesis of Silver (I) Oxide [42]

A solution of 10 g of sodium hydroxide in 100 mL of hot water was added to a solution of 30 g of silver nitrate in 100 mL of hot water. The brown precipitate of silver (I) oxide was washed with 5 × 50 mL of warm water and once with 50 mL of ethanol by decantation. The solid was filtered off, washed with ethanol and dried under vacuum.

3.3.2. General Procedure for Oxidation

A solution of **3a**–**j** (1.8 mmol) in dry diethyl ether (50 mL) was prepared in a flask covered with aluminum foil. Silver (I) oxide (3 mmol) and anhydrous sodium sulfate (25 mmol) were added, and the suspension was stirred rapidly overnight. The slurry was subsequently filtered over a pad of Celite® and the liquid filtrate was evaporated to dryness to obtain compounds **6a**–**j** as colorful solids.

All oxidation products **6a**–**j** are known and their spectroscopic data match previously reported data [1,6,13,43,44]. Characteristic spectroscopic details of **6a**–**j** can be found in the Supplementary Materials.

3.4. Antimicrobial Activity Testing

General Procedure for Bioscreening

A stock solution was prepared by dissolving the selected compound in 1 mL of ultrapure acetone in a plastic Eppendorf tube (using a sterilized pipette tip). Agar plates were then prepared, and the bacteria—*Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*—were applied via the spread plate technique. A total of 20 µL of the stock solutions were applied to small, sterile filter discs. Negative control discs were prepared by pipetting 20 µL of acetone onto the respective filter discs. All discs were left to dry in labelled glass Petri dishes with their lids on. Once the filter discs were dry and the bacteria suspension had settled into the agar, the discs were placed onto the plates using sterilized tweezers. Each plate consisted of four 'test discs', one negative control disc and one antibiotic disc (positive control). Fosfomycin (200 µg), vancomycin (30 µg) and nalidixic acid (30 µg) discs were used as reference antibiotics on *S. aureus*, *E. faecium* and *E. coli* and *K. pneumoniae* and *P. aeruginosa*, respectively.

4. Conclusions

In conclusion, a library of 2-acylated 1,4-hydroxynaphthoquinones was generated in moderate yields via the photo-Friedel–Crafts acylation of 1,4-naphthoquinone and readily available aldehydes. The easy procedure makes this methodology attractive for scale-up and examples of technical-scale photoacylations in concentrated sunlight have already been reported [45,46]. Subsequent thermal oxidation furnished the corresponding 2-acylated 1,4-naphthoquinones in high to excellent yields. As both processes have been separately realized under continuous-flow conditions [41,47,48], they may be subsequently combined in series through telescoping [49]. Antibiotic screening conducted with most of the compounds synthetized revealed strong activity against *S. aureus*, justifying further medicinal chemistry studies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/photochem4040031/s1, General methods, experimental setups and spectroscopic data. Figure S1. UVA photoacylations in the Rayonet reactor prior to (left) and

after irradiation (center and right). Figure S2. Solar photoacylations prior to (left) and after (center and right) exposure.

Author Contributions: A.M. (Alexis Mercier), A.M. (Alizée Monet) and M.A.Y. conducted the research and collected the data; A.M. (Alexis Mercier) drafted the manuscript; M.I.H. supervised and assisted with the biological screening; M.O. secured the funding, supervised the chemical research and wrote the final manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: All data is available on request from the corresponding author.

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