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Photoacylations of 2-substituted 1,4-naphthoquinones: a concise access to biologically active quinonoid compounds

Prashant A. Waske,[a] Jochen Mattay[a,*] and Michael Oelgemöller[b,*]

[a]*Organische Chemie I, Fakultät für Chemie, Universität Bielefeld, Postfach 10 01 31, D-33501 Bielefeld, Germany*
[b]*Dublin City University, School of Chemical Sciences and National Institute for Cellular Biotechnology, Glasnevin, Dublin 9, Ireland*

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Abstract—Photochemical acylations of 2-substituted-1,4-naphthoquinones with various aldehydes furnished acylated hydroquinones and acylated quinones in moderate to good combined yields. All reactions are easily performed and open a rapid access to biologically active compounds. For the 2-methyl-1,4-naphthoquinone/butyraldehyde pair, a novel *tri*-keto compound has been additionally isolated.
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Acylated quinone derivatives based on 2-substituted 1,4-naphthoquinones represent an important class of natural products.[1] A versatile pathway for the construction of these compounds is the photochemical acylation of quinones with aldehydes, for which we introduced the term 'photo Friedel–Crafts acylation'.[2,3] This extremely useful photoreaction was discovered by Heinrich Klinger in 1888, who exposed solutions of the starting materials to natural sunlight over long periods of time.[4] During the last few decades, a number of additional reports appeared in the literature, but most of the studies focused on unsubstituted 1,2- or 1,4-quinones.[5] In contrast, reports based on 2-substituted 1,4-naphthoquinones remained rare.[6]

In order to fill this gap, we have studied photochemical acylation reactions of 2-methyl- and 2-methoxy-1,4-naphthoquinone with different aliphatic as well as aromatic aldehydes. The selected compounds provide a convenient access to potent antimalarials as **M5**,[7] quinonoid antibiotics as 2-dodecanoyl-3-hydroxy-1,4-naphthoquinone[8] or pesticides as the important acaricide acequinocyl (Fig. 1),[9] respectively. To the best of our knowledge, only a single brief example of a photoacylation involving 2-methyl-1,4-naphthoquinone has been reported so far by Schenck and Koltzenburg.[6a]

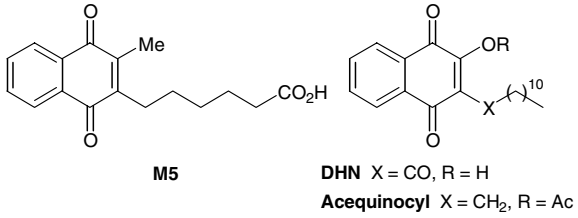
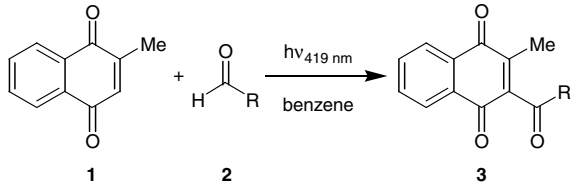


Figure 1. Structures of **M5**, 2-dodecanoyl-3-hydroxy-1,4-naphthoquinone (DHN) and acequinocyl.

Irradiations of 2-methyl-1,4-naphthoquinone **1** with various aliphatic as well as aromatic aldehydes gave the corresponding acylated quinones **2** in moderate yields of 23–49% (Scheme 1; Table 1)[10] indicating that the 'hydroquinones' formed initially are oxidized during workup. All compounds showed characteristic ^{13}C



Scheme 1. Photoacylations of 2-methyl-1,4-naphthoquinone **1**.

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* Corresponding authors. Tel.: +49 521 106 2072; fax: +49 521 106 6417 (J.M.); tel.: +353 1 700 5312; fax: +353 1 700 5503 (M.O.); e-mail addresses: mattay@uni-bielefeld.de; michael.oelgemoeller@dcu.ie

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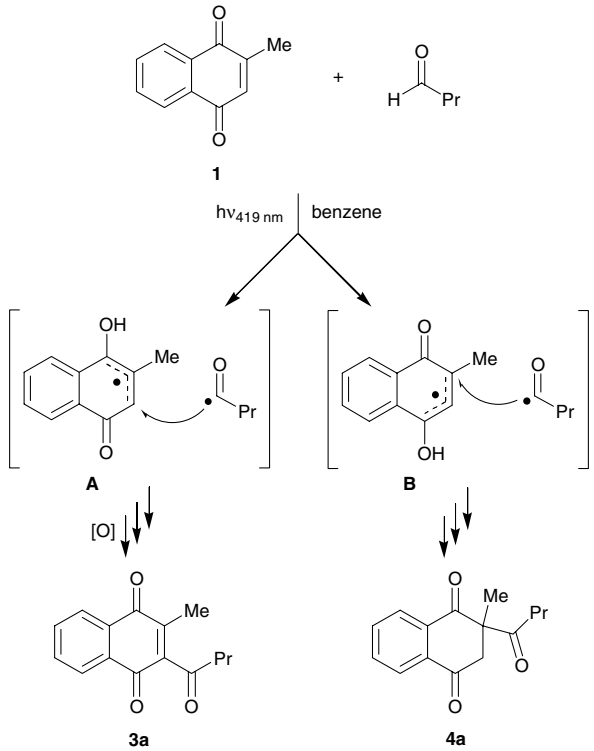
Table 1. Isolated product yields for 2-methyl-1,4-naphthoquinone **1** and 2-methoxy-1,4-naphthoquinone **5**

Entry	R	Time [h][a]	**3** or **6** [%]	**4** or **7** [%]
a	Pr	15	49 (**3**)	10 (**4**)
b	*i*-Pr	18	36 (**3**)	—
c	$C_{11}H_{23}$	12	39 (**3**)	—
d	Ph	18	23 (**3**)	—
e	*p*-$MeOC_6H_4$	12	42 (**3**)	—
f	*p*-MeC_6H_4	12	35 (**3**)	—
g	Pr	12	24 (**6**)	11 (**7**)
h	$C_{11}H_{23}$	12	—	23 (**7**)

[a] Until starting material is consumed.

NMR resonances between 183 and 186 ppm for their quinonoid carbons. Hence, this protocol represents a straightforward pathway to 2-acyl-3-methyl-1,4-quinones. Solely with *p*-methoxybenzaldehyde, larger amounts (ca. 10–20%) of the regioisomeric monoesters of **1** were detected in the crude ^{1}H NMR spectrum but could not be isolated in sufficient amounts and purities. Their formation accounts for the more electrophilic character of the corresponding *p*-methoxybenzoyl radical.[5a,11]

Another exceptional case was the reaction of **1** with butyraldehyde and the unusual *tri*-keto compound **4a** was obtained in 10% yield next to 49% of the acylated quinone **3a** (Scheme 2). The structure of **4a** was unambiguously confirmed by 2D-NMR techniques such as ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMBC and HSQC analysis, respectively. In $CDCl_3$, its ^{1}H NMR spectrum showed



Scheme 2. Photoacylations of 2-methyl-1,4-naphthoquinone **1** with butyraldehyde.

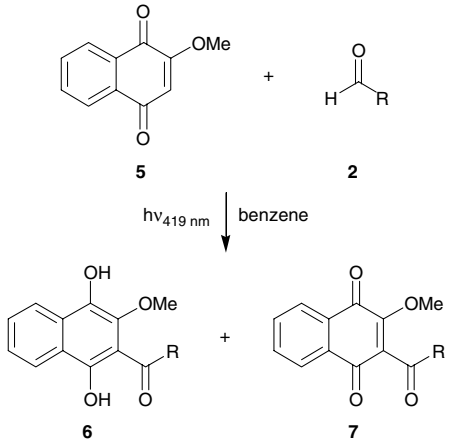
two clearly separated doublets for the CH_2 group at 2.73 and 3.36 ppm with a large ^2J coupling of 16.9 Hz.[12] The formation of **4a** may be best explained by the following *in-cage* scenario: hydrogen transfer from the aldehyde to the excited quinone **1*** leads to the corresponding semiquinone radical pair **A** and **B**. Radical combination with the acyl radical followed by tautomerization affords the observed products **3a** (after further oxidation) and **4a**.

An alternative *out-of-cage* attack of the acyl radical (not shown) to a ground state quinone **1** would lead preferentially to the acylated quinone **3a** via the most stable radical intermediate. Steric hindrance by the methyl group in **1** would furthermore prevent an addition at position 2. Thus, the isolation of **4a** suggests that an *in-cage* mechanism is indeed operating, at least in parts.[13]

The reaction of 2-methoxy-1,4-naphthoquinone **5** with butyraldehyde furnished a mixture of the monoacylated hydroquinone **6a** and its acylated quinone **7a** (Scheme 3, Table 1).[14] The phenolic protons of **6a** gave broad singlets at 5.60 and 13.89 ppm, which were unambiguously assigned via H–D exchange with D_2O. Surprisingly, compound **6a** remained rather stable in solution but was rapidly oxidized in the solid state to its corresponding quinone **7a**. Irradiation of **5** in the presence of dodecanal solely gave the acylated quinone **7b**, which represents an important key intermediate for the synthesis of the antibiotic.

As for **1**, the presence of the electron donating *methoxy* group obviously makes the primary hydroquinones **6** sensitive towards oxidation by oxygen.[6b,15] The lack of any bisacylation products, that is acylated monoesters formed through secondary O-acylation, supports the assumption that the quinones **7** are indeed formed during workup.

In conclusion, the photochemical acylation of 2-substituted 1,4-naphthoquinones proceeds with the formation of acylated hydroquinones and/or quinones in moderate to good yields. The photoacylation protocol could be



Scheme 3. Photoacylations of 2-methoxy-1,4-naphthoquinone **5**.

used as a straightforward preparation of synthetically important precursors to quinonoid pharmaceuticals and agrochemicals.

Acknowledgements

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10. General procedure for irradiation: In a typical photochemical experiment, a solution of 1 mmol of the naphthoquinone and 9 mmol of aldehydes in 60 ml of dry benzene was split over 5 Pyrex tubes (capacity 12 ml each), degassed with argon and irradiated for 12–18 h using a Rayonet Photochemical reactor (RPR–100; Southern New England Ultraviolet Company) equipped with RPR 4190 Å lamps ($\lambda_{max} = 419 \pm 15$ nm). The reaction was continued until GC analysis indicated complete consumption of the quinone. The combined solutions were evaporated under vacuum and the crude residue was purified by flash column chromatography (silica gel, 30% ethyl acetate in cyclohexane), followed, if required, by preparative HPLC. Selected physical and spectral data for the product 2-butyryl-3-methyl-1,4-naphthoquinone **3a**: light yellow solid, mp 76–79 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.72 (dq, 2H, $J = 7.5$ Hz, CH_2CH_3), 2.06 (s, 3H, CH_3), 2.69 (t, 2H, $J = 7.5$ Hz, $COCH_2$), 7.74 (m, 2H, Ar-H), 8.03 (m, 1H, Ar-H), 8.08 ppm (m, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.1$ (CH_3), 13.7 (CH_3), 16.5 (CH_2), 46.1 (CH_2), 126.1 (CH), 126.6 (CH), 131.4 (C), 131.7 (C), 134.0 (CH), 134.1 (CH), 142.4 (C), 145.7 (C), 183.5 (C=O), 185.1 (C=O), 203.9 ppm (C=O). IR (KBr): $\nu = 2961$, 2935, 2875, 2362, 1702, 1663, 1594, 1458, 1375, 1326, 1289, 1151, 1006, 958, 793, 703 cm^{-1}. MS (EI): *m/z* (%) = 242 (M^+, 80), 228 (4), 227 (23), 200 (20), 199 (95), 196 (2), 174 (12), 171 (100), 143 (21), 116 (12), 115 (69), 89 (17), 89 (16), 76 (18), 67 (16), 58 (14), 43 (36). HR-MS (EI^+): 242.09425 (calcd 242.09429).
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12. Selected physical and spectral data for the product 2-butyryl-3-methyl-2,3-dihydro-1,4-naphthoquinone **4**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.68$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 1.36–1.46 (m, 2H, CH_2CH_3), 1.58 (s, 3H, CH_3), 2.30 (ddd, 1H, $J = 17.9$, 7.8, 6.2 Hz, $COCH_2$), 2.46 (ddd, 1H, $J = 17.9$, 7.7, 6.6 Hz, $COCH_2$), 2.73 (d, 1H, $J = 16.9$ Hz, CH_2), 3.36 (d, 1H, $J = 16.9$ Hz, CH_2), 7.69 (m, 2H, Ar-H), 7.98 (m, 1H, Ar-H), 8.06 ppm (m, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.3$ (CH_3), 16.9 (CH_2), 20.0 (CH_3), 39.2 (CH_2), 46.9 (CH_2), 65.1 (C), 126.7 (CH), 127.2 (CH), 133.9 (C), 134.2 (CH), 134.7 (CH), 135.3 (C), 193.4 (C=O), 195.3 (C=O), 206.8 ppm (C=O). IR (KBr): $\nu = 2963$, 2934, 2874, 1687, 1665, 1594, 1458, 1379, 1286, 1265, 1216, 978 cm^{-1}. MS (EI): *m/z* (%) = 244 (M^+, 16), 228 (3), 201 (5), 185 (12), 175 (14), 174 (100), 159 (91), 159 (9), 149 (11), 131 (6), 128 (5), 117 (4), 105 (10), 91 (5), 76 (14), 71 (45), 55 (2), 43 (66). HR-MS (EI^+): 244.10967 (calcd 244.10994).

13. Both, *in-cage* and *out-of-cage* mechanisms have been described in the literature and both mechanisms operate more-or-less simultaneously depending on the specific reaction conditions of the irradiation experiment (i.e., temperature, solvent, quinone/aldehyde applied).[5a] Further mechanistic investigations are currently carried out for the 2-methyl-1,4-naphthoquinone/butyraldehyde using either thermally or chemically generated acyl radicals.
14. Selected physical and spectral data for the product 1-(1,4-dihydroxy-3-methoxy-naphthalen-2-yl)-butan-1-one **6a**: brown solid, mp 109–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.76 (dq, 2H, $J = 7.5$ Hz, CH_2CH_3), 3.11 (t, 2H, $J = 7.5$ Hz, $COCH_2$), 3.79 (s, 3H, OCH_3), 5.60 (s, 1H, OH), 7.47 (ddd, 1H, $J = 1.3$, 6.9, 8.2 Hz, Ar-H), 7.63 (ddd, 1H, $J = 1.3$, 6.9, 8.2 Hz, Ar-H), 8.08 (d, 1H, $J = 8.1$ Hz, Ar-H), 8.38 (d, 1H, $J = 8.1$ Hz, Ar-H), 13.89 ppm (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (CH_3), 18.3 (CH_2), 44.3 (CH_2), 62.3 (OCH_3), 108.8 (C), 121.4 (CH), 123.1 (C), 124.5 (CH), 125.6 (CH), 128.4 (C), 129.9 (CH), 135.9 (C), 138.4 (C), 157.3 (C), 206.3 ppm (C=O). IR (KBr): $\nu = 3427$, 2964, 2937, 2365, 1708, 1679, 1626, 1600, 1570, 1454, 1399, 1332, 1772, 1216, 1124, 1046, 911, 729 cm^{-1}. MS (EI): m/z (%) = 260 (M^+, 94), 258 (52), 257 (6), 246 (36), 231 (34), 230 (57), 227 (57), 217 (27), 209 (14), 199 (19), 190 (66), 181 (11), 174 (16), 163 (22), 159 (13), 128 (12), 115 (21), 105 (37), 89 (22), 79 (4), 71 (77). Selected physical and spectral data for the product 2-butyryl-3-methoxy-1,4-naphthoquinone **7a**: brown solid, mp 144–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.73 (dq, 2H, $J = 7.5$ Hz, CH_2CH_3), 2.73 (t, 2H, $J = 7.5$ Hz, $COCH_2$), 4.10 (s, 3H, OCH_3), 7.74 (m, 2H, Ar-H), 8.04 (m, 2H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 16.6 (CH_2), 46.9 (CH_2), 61.4 (OCH_3), 126.1 (CH), 126.6 (CH), 130.0 (C), 131.0 (C), 131.2 (C), 133.8 (CH), 134.6 (CH), 155.3 (C), 181.5 (C=O), 183.8 (C=O), 202.0 (C=O). IR (KBr): $\nu = 3441$, 2699, 2877, 2359, 1709, 1662, 1581, 1440, 1274, 1071, 902, 735 cm^{-1}. MS (EI): m/z (%) = 258 (M^+, 4), 257 (1), 243 (8), 230 (6), 228 (9), 215 (100), 209 (1), 187 (71), 173 (10), 167 (5), 149 (4), 129 (4), 104 (23), 89 (7), 87 (2), 76 (21), 71 (13). HR-MS (EI^+): 258.08939 (calcd 258.08921).
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