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Photochemical Synthesis of 3-Alkynals from 1-Alkynoxy-9,10-anthraquinones

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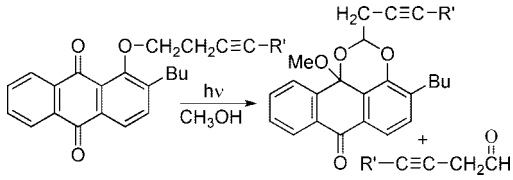
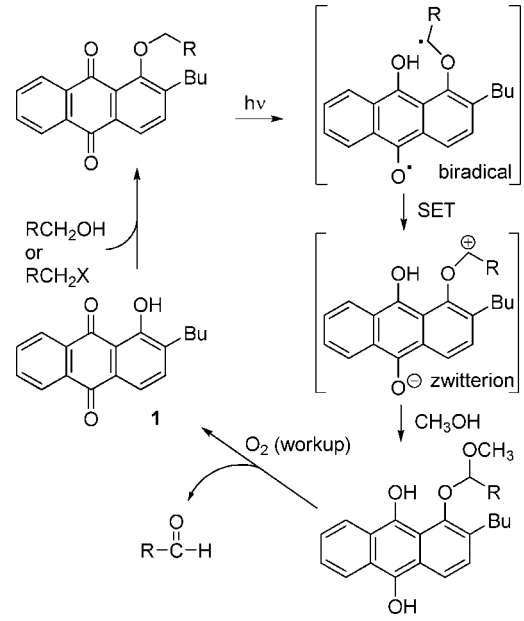


Photolysis of 1-(3-alkynoxy)-9,10-anthraquinones in deoxygenated methanol leads to moderate yields (35−45%) of 3-alkynals along with the unexpected formation of diacetals. Reaction of these 3-alkynals with Grignard and Wittig reagents occurs nearly quantitatively without rearrangement to their 2,3-dienal isomers.

3-Alkynals have the potential to play an important role in synthesis by selective reaction of their isolated functional groups. They possess a triple bond, for example, that would be expected to undergo cyclization reactions,[1] and a carbonyl that would be expected to react with a variety of nucleophiles including Wittig reagents[2] and enolates.[3] Early attempts to prepare 3-alkynals by the hydrolysis of vinyl ethers[4] and acetals,[5] and the periodate oxidation of glycols,[6] were only marginally successful because the target compounds were often contaminated by their conjugated 2,3-dienal isomers, presumably formed by rearrangement under the reaction conditions. More recently, 3-alkynals have been prepared in fairly high purity by using a mild chemoenzymatic oxidation−hydrocyanation protocol[7] and the Dess−Martin oxidation.[8]

SCHEME 1. Photochemical Synthesis of Aldehydes



Since alkanals can be prepared in isolated yields of 60−80% in the absence of strong acids and strong oxidants by using a photochemistry process developed in our laboratory (Scheme 1),[9] we were confident that this method could provide another entry into 3-alkynals without significant rearrangement to their corresponding 2,3-dienals. In this work we describe the synthesis of 3-alkynals using this photochemical method, which is believed to occur through biradical and zwitterion intermediates.[9d] Oxidation of the anthrahydroquinone photoproduct and hydrolysis of its acetal occur during the workup upon exposure to oxygen.[9d]

Beginning with 1-hydroxy-2-butyl-9,10-anthraquinone (**1**), which can be made from commercially available 1-hydroxy-9,10-anthraquinone by using the Marshalk reaction,[10] and readily available 3-alkyn-1-ols, anthraquinones **2a** and **2b** were obtained in isolated yields of 65% and 63%, respectively, using the Mitsunobu reaction.[11] (Scheme 2). Irradiation of **2** in the absence of oxygen with 300−370 nm light gave anthraquinone **1**, the target 3-alkynals **3**, and diacetals **4** in isolated yields of 50−55%,

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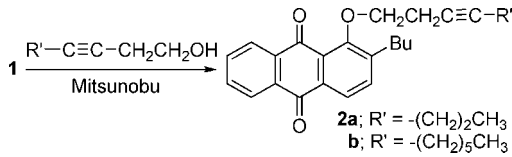
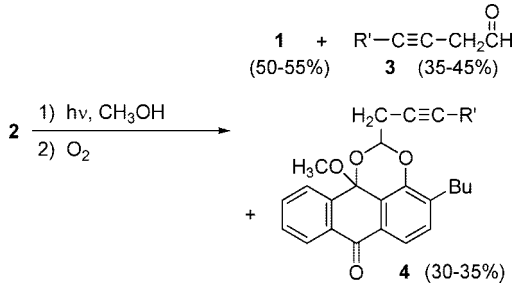
SCHEME 2. Synthesis of 3-Alkynal Precursors



SCHEME 3. Photolysis of Anthraquinones 2 in Deoxygenated Methanol



35−45%, and 30−35%, respectively (Scheme 3). Only trace amounts of 2,3-dienals were formed as shown in the proton NMR spectrum of 3-decynal in Figure 1 (left spectrum), which displays a very weak doublet (J = 7.24 Hz) for the aldehydic proton of 2,3-decadienal at 9.53 ppm with an integration of less than 2% relative to the triplet at 9.60 ppm.

The lower than expected yields of 3-alkynals **3** can be attributed to the formation of significant amounts of diacetals **4**. In our earlier work using this photochemistry alkanals were obtained in isolated yields of 60−80% without the formation of significant amounts of the corresponding diacetals.[9a] Interestingly, Jones and Brinson obtained similar yields of α,β-unsaturated aldehyde **6** and diacetal **7** when anthraquinone **5** was irradiated at wavelengths above 350 nm in degassed methanol (Scheme 4).[12] It is not clear what role the triple and double bonds are playing that leads to these diacetal byproducts. Unlike diacetal **7**, though, diacetal **4** does not form more aldehyde when irradiated at shorter wavelengths.[13]

Since diacetals **4** only slowly hydrolyzed on a silica gel column, it was possible to obtain them in fairly high purity by

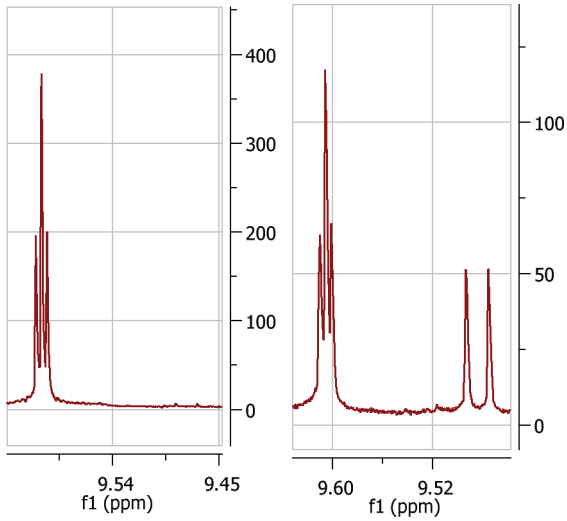
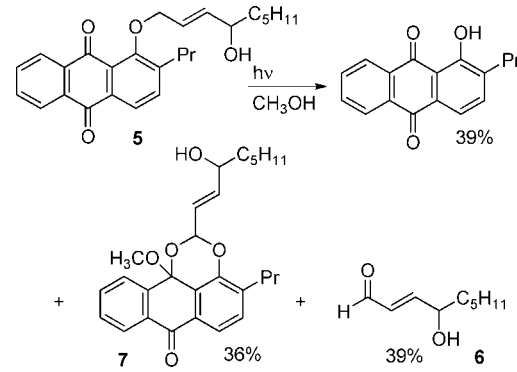
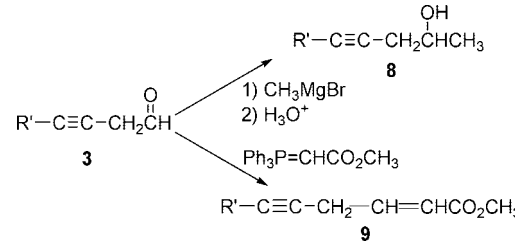


FIGURE 1. ^{1}H NMR spectra of the aldehydic proton of 3-decynal before (left) and after (right) a solution of the compound was stirred for 10 min in the presence of silica gel. The appearance of the doublet in the spectrum to the right shows that extensive rearrangement to 2,3-decadienal has occurred.

SCHEME 4. Photolysis of Anthraquinone 5 in Deoxygenated Methanol[12]



SCHEME 5. Reaction of 3-Alkynals with Grignard and Wittig Reagents



using flash chromatography. In an attempt to increase the yields of 3-alkynals by preventing the formation of their corresponding diacetals, the photolysis of **2b** was conducted in 90% aqueous THF. Unfortunately, the yield of 3-decynal did not increase significantly in this medium.

Not surprisingly, 3-alkynals rearrange in the presence of silica gel to their corresponding 2,3-dienals as shown in Figure 1 for 3-decynal. Therefore, ether solutions of **3**, which were obtained by vacuum distillation from their reaction mixtures, but were not further purified, were reacted with methylmagnesium bromide to give the corresponding 4-alkyn-2-ols **8** in overall yields of 35−40% from **2** without significant amounts of 3,4-alkadien-2-ols. Similar results were obtained when alkynals **3** were reacted with methyl (triphenylphosphoranylidene)acetate to form their corresponding methyl 2-alken-5-ynoate esters **9** with trans:cis ratios of ca. 7:1. One may conclude then that strong nucleophiles undergo carbonyl addition to **3** in high yield without prior rearrangement of these 3-alkynals to their 2,3-dienal isomers (Scheme 5).

In conclusion, 3-alkynals with only trace amounts of their 2,3-dienal isomers can be prepared in moderate yield by using a photochemical process that employs a 1-alkynoxy-9,10-anthraquinone template. Comparable yields of diacetal byproducts are also obtained. Reaction of these 3-alkynals with Grignard and Wittig reagents occurred almost quantitatively without prior rearrangement to their 2,3-dienals.

Experimental Section

3-Heptynal:[4d] ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.59 (t, 1H, J = 1.9 Hz), 3.22 (dt, 2H, J = 1.9, 2.5 Hz), 2.16 (tt, 2H, J = 2.5, 7.0

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(13) Diacetal **4b** was irradiated with 280−370 nm light using a quartz container for 24 h without appreciable reaction. Brinson and Jones found that diacetal **7** rapidly produces **6** and 1-hydroxy-2-propyl-9,10-anthraquinone when irradiated in methanol at 366 nm.

Hz), 1.51 (sext, 2H, $J = 7.3$ Hz), 0.97 (t, 3H, $J = 6.8$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 86.4, 70.3, 34.8, 22.6, 21.7, 14.4 ppm.

3-Decynal:[5b] ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.60 (t, 1H, $J =$ 1.9 Hz), 3.23 (dt, 2H, $J = 1.9$, 2.5 Hz), 2.20 (tt, 2H, $J = 2.5$, 7.0 Hz), 1.50 (br pent, 2H, $J = 7.3$ Hz), 1.42−1.26 (m, 6H), 0.89 (t, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 86.3, 70.2, 34.9, 31.5, 28.9, 28.7, 22.7, 19.0, 14.2 ppm.

1-(3-Heptynoxy)-2-butyl-9,10-anthraquinone (2a).[11] To 35 mL of dry THF in a 50 mL round-bottomed flask was added 2-butyl-1-hydroxy-9,10-anthraquinone (0.187 g, 6.68 mmol), Ph_3P (2.75 g, 10.4 mmol), and 3-heptyn-1-ol (1.39 g, 12.4 mmol). To the resulting solution cooled in a bath at −10 °C under N_2 was added diisoproyl azodicarboxylate (2.50 g, 12.4 mmol) dropwise over 30 min. The bath was removed and the reaction mixture was stirred at room temperature for 48 h. The bulk of the THF was removed in a rotary evaporation under reduced pressure and the residue was combined with 50 mL of boiling hexane. The solid residue, consisting of the hydrazine and Ph_3PO byproducts, was removed by hot filtration. The solvent in the filtrate was removed in the rotary evaporator under reduced pressure giving a viscous red liquid, which was dissolved in 15 mL of hot methanol. On cooling the desired product was obtained as yellow crystals (1.63 g, 65%): mp 92−93 °C; IR (KBr) 2957, 2930, 2873, 1671, 1582, 1566, 1468, 1326, 1283, 1255, 1239, 1045, 1030, 979, 715 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.26−8.20 (m, 2H), 8.06 (d, 1H, $J = 7.9$ Hz), 7.78−7.71 (m, 2H), 7.61 (d, 1H, $J = 7.9$ Hz), 4.06 (t, 2H, $J = 7.0$ Hz), 2.86 (m, 4H), 2.13 (tt, 2H, $J = 2.2$, 7.0 Hz), 1.65 (quintet, 2H, $J = 7.7$ Hz), 1.51 (sextet, 2H, $J = 7.1$ Hz), 1.42 (sextet, 2H, $J = 7.2$ Hz), 0.96 (t, 6H, $J = 7.3$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 182.5, 157.3, 145.5, 135.4, 134.8, 133.9, 133.6, 133.3, 132.6, 127.1, 126.5, 125.5, 123.4, 81.7, 76.3, 72.9, 32.3, 30.0, 22.6, 22.3, 20.7, 20.6, 13.9, 13.4 ppm. Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.19; H, 7.00. Found: C, 80.45; H, 6.77.

1-(3-Decynoxy)-2-butyl-9,10-anthraquinone (2b).[11] The procedure for preparing anthraquinone **2a** was used giving anthraquinone **2b** as yellow crystals (63%): mp 64−65 °C; IR (KBr) 2958, 2934, 2872, 2859, 1673, 1580, 1567, 1466, 1326, 1281, 1254, 1192, 1045, 1028, 978, 865, 795, 716 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.26−8.20 (m, 2H), 8.06 (d, 1H, $J = 7.9$ Hz), 7.78−7.70 (m, 2H), 7.61 (d, 1H, $J = 7.9$ Hz), 4.06 (t, 2H, $J = 7.0$ Hz), 2.86−2.81 (m, 4H), 2.14 (tt, 2H, $J = 2.3$, 7.1 Hz), 1.69−1.61 (m, 2H), 1.51−1.21 (m, 10H), 0.96 (t, 3H, $J = 7.3$ Hz), 0.87 (t, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 182.6, 157.3, 145.4, 135.4, 134.8, 133.9, 133.6, 133.3, 132.6, 127.1, 126.4, 125.5, 123.4, 81.9, 76.1, 73.0, 32.3, 31.3, 30.0, 28.9, 28.5, 22.6, 22.4, 20.6, 18.7, 14.0, 13.9 ppm. Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.74; H, 7.74. Found: C, 80.64; H, 7.59.

Methyl *trans*-2-nonen-5-ynoate: colorless oil; IR (neat) ν 2963, 2931, 2876, 2213, 1731, 1661, 1436, 1276, 1170, 1039, 984 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.94 (1 H, dt, $J = 15.2$, 5.00 Hz), 6.16 (1 H, dt, $J = 15.2$, 2.1 Hz), 3.75 (3 H, s), 3.12−3.09 (2 H, m), 2.18 (2 H, tt, $J = 7.0$, 2.4 Hz), 1.54 (2 H, sext, $J = 7.2$ Hz), 0.99 (3 H, t, $J = 7.2$) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.8, 143.8, 122.1, 84.2, 74.5, 51.4, 22.3, 22.0, 20.7, 13.4 ppm; HRMS [EI$^+$] found 166.0994, $C_{10}H_{14}O_2$ requires 166.0994.

Methyl *trans*-2-dodecen-5-ynoate: colorless oil; IR (neat) ν 2960, 2928, 2857, 2230, 1729, 1661, 1274, 1168, 984 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.93 (1 H, dt, $J = 15.4$, 5.04 Hz), 6.15 (1 H, dt, $J = 15.4$, 2.0 Hz), 3.74 (3 H, s), 3.10 (2 H, m), 2.19 (2 H, tt, $J = 7.0$, 2.4 Hz), 1.51 (2 H, pent, $J = 7.3$ Hz), 1.42−1.26 (6 H, m), 0.89 (3 H, t, $J = 6.8$ Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.8, 143.7, 122.1, 84.4, 74.3, 51.5, 31.3, 28.9, 28.6, 22.5, 22.0, 18.7, 14.0 ppm; HRMS [EI$^+$] found 208.1461, $C_{13}H_{20}O_2$ requires 208.1463.

Diacetal 4a: off-white solid; IR (neat) ν 3072, 2956, 2252, 1728, 1675, 1591, 1440, 1260, 1122, 1058, 1039, 1016, 900, 772, 710 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.13 (1 H, br d, $J = 7.6$ Hz), 7.85 (1 H, br d, $J = 7.5$ Hz), 7.59 (1 H, br t, $J = 7.6$ Hz), 7.57 (1 H, d, $J = 7.8$ Hz), 7.51 (1 H, br t, $J = 7.5$ Hz), 7.23 (1 H, d, $J =$ 7.8 Hz), 5.83 (1 H, br t, $J = 5.5$ Hz), 3.06 (3 H, s), 2.95−2.91 (2 H, m), 2.65 (2 H, br t, $J = 7.6$ Hz), 2.21 (2 H, tt, $J = 6.8$, 2.4 Hz), 1.62−1.52 (4 H, m), 1.36 (2 H, sext, $J = 7.4$ Hz), 1.03 (3 H, t, $J = 7.4$ Hz), 0.93 (3 H, t, $J = 7.4$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 148.7, 137.4, 136.0, 133.1, 131.4, 130.4, 129.9, 129.2, 127.7, 125.0, 123.2, 119.6, 92.4, 91.9, 82.8, 73.7, 49.1, 31.5, 29.4, 25.5, 22.4, 22.3, 20.8, 13.9, 13.4 ppm; HRMS [EI$^+$] found 404.1992, $C_{26}H_{28}O_4$ requires 404.1988.

Diacetal 4b: off-white solid; IR (neat) ν 3073, 2954, 2927, 2857, 2249, 1728, 1677, 1591, 1441, 1258, 1059, 1040, 1016, 944, 798, 707 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.13 (1 H, dd, $J = 7.6$, 1.2 Hz), 7.85 (1 H, dd, $J = 7.6$, 1.2 Hz), 7.59 (1 H, dt, $J = 7.6$, 1.6 Hz), 7.57 (1 H, d, $J = 7.6$ Hz), 7.51 (1 H, dt, $J = 7.6$, 1.2 Hz), 7.23 (1 H, br d, $J = 7.6$ Hz), 5.83 (1 H, dd, $J = 6.0$, 4.8 Hz), 3.06 (3 H, s), 2.94−2.91 (2 H, m), 2.65 (2 H, t, $J = 7.6$ Hz), 2.23 (2 H, tt, $J = 6.8$, 2.4 Hz), 1.62−1.50 (4 H, m), 1.46−1.26 (8 H, m), 0.93 (3 H, t, $J = 7.4$ Hz), 0.89 (3 H, t, $J = 7.2$ Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 184.6, 148.7, 137.4, 136.0, 133.1, 131.4, 130.4, 129.9, 129.2, 127.7, 125.0, 123.2, 119.6, 92.4, 91.9, 82.9, 73.5, 49.0, 31.5, 31.4, 29.4, 28.9, 28.6, 25.5, 22.6, 22.4, 18.7, 14.0, 13.9 ppm; HRMS [EI$^+$] found 446.2461, $C_{29}H_{34}O_4$ requires 446.2457.

4-Octyn-2-ol: colorless oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.91 (1 H, br s), 2.38 (1 H, ddt, $J = 16.4$, 4.8, 2.5 Hz), 2.28 (1 H, ddt, $J = 16.4$, 6.8, 2.4 Hz), 2.16 (2 H, tt, $J = 7.2$, 2.4 Hz), 2.02 (1 H, br d, $J = 2.8$ Hz), 1.52 (2 H, sext, $J = 7.3$ Hz), 1.24 (3 H, d, $J =$ 6.4 Hz), 0.98 (3 H, t, $J = 7.4$ Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 83.1, 76.2, 66.5, 29.4, 22.4, 22.1, 20.7, 13.5 ppm.

4-Undecyn-2-ol: colorless oil; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.99 (1 H, br sext, $J = 6.0$ Hz), 2.37 (1 H, ddt, $J = 16.4$, 4.9, 2.4 Hz), 2.27 (1 H, ddt, $J = 16.4$, 6.7, 2.4 Hz), 2.17 (2 H, tt, $J = 7.2$, 2.4 Hz), 2.03 (1 H, br s), 1.49 (2 H, pent, $J = 7.1$ Hz), 1.41−1.27 (6 H, m), 1.24(3 H, d, $J = 6.4$ Hz), 0.89 (3 H, t, $J = 7.0$ Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 83.3, 76.0, 66.5, 31.3, 29.4, 28.9, 28.5, 22.5, 22.1, 18.7, 14.0 ppm.

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Supporting Information Available: General procedures; proton and carbon NMR spectra of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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