Photochemistry in supercritical carbon dioxide. The benzophenone-mediated addition of aldehydes to α,β-unsaturated carbonyl compounds

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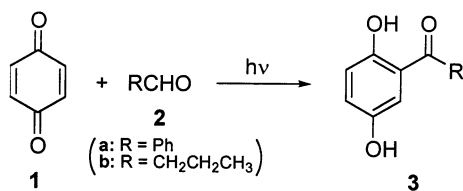[b]Department of Chemistry, Iowa State University, Ames, IA 50011, USA

Abstract—The photo-induced addition of aldehydes to α,β-unsaturated carbonyl compounds is an effective, 'environmentally benign' method for the synthesis of 2-acyl-1,4-hydroquinones (from quinones) and 1,4-diketones (from enones). This process has been improved by eliminating benzene as a solvent and replacing it with supercritical carbon dioxide. Highest yields were obtained at higher CO_2 pressures, or with the addition of 5% t-butyl alcohol as co-solvent. © 2001 Elsevier Science Ltd. All rights reserved.
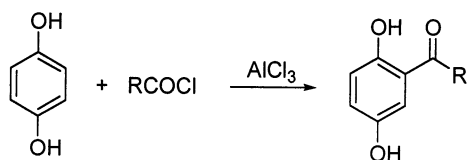
In 1992, Kraus and co-workers reported a general photochemical process for the synthesis of acylhydroquinones, starting from the corresponding aldehyde and quinone (Scheme 1).[1] The significance of this process is that it provides a viable, 'environmentally benign' alternative[2] to the Friedel–Crafts acylation reaction (Scheme 2), which typically requires (a) the use of corrosive acid chlorides, (b) use of strong Lewis acids ($AlCl_3$, $TiCl_4$, etc.), and often (c) the use of hazardous solvents.

A likely mechanism for this process is depicted in Scheme 3.[2] Irradiation yields the quinone triplet excited state. Because the C–H bond of the formyl group is weak (<90 kcal/mol), this hydrogen is readily abstracted by the excited state quinone yielding radical pair **4**. Radical–radical coupling, followed by enolization, yields **3**. In instances where yields were poor, addition of catalytic quantities of benzophenone resulted in a dramatic improvement.[3] (Details regarding the mechanism were not reported; presumably the benzophenone is serving as a sensitizer.)
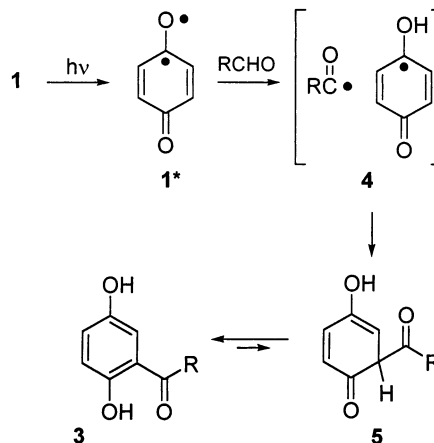

Scheme 1.

Scheme 2.

Scheme 3.

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Table 1. Benzophenone-mediated reaction of 1,4-benzoquinone (**1**) with benzaldehyde in PhH and several alcoholic co-solvents (time: 3 days)

Solvent	Unreacted **1** (%)	Yield **3a** (%)	Yield 1,4-hydroquinone (%)
PhH	19	56	0
PhH + 5% MeOH	0	19	46
PhH + 5% EtOH	0	0	60
PhH + 5% i-PrOH	0	13	40
PhH + 5% t-BuOH	36	46	0

From an environmental perspective, one drawback to the Kraus procedure involves the use of benzene as a solvent. Further gains in pollution prevention could be realized by replacing benzene with a more 'environmentally benign' solvent. This paper describes the use of supercritical carbon dioxide (SC-CO_2)[4–7] as a viable alternative to benzene for the Kraus photochemical acylation process.

Kraus reports that in benzene solvent, the photolysis of benzaldehyde and 1,4-benzoquinone produces the 2-benzoyl-1,4-hydroquinone (**3a**) in 60% yield.[1] Under the reported conditions of these experiments, the concentrations of 1,4-benzoquinone and benzaldehyde were 0.2 and 1.4 M, respectively. Because SC-CO_2 is non-polar, such high concentrations of these polar substrates could not be achieved. Hence, initial experiments were designed to repeat the Kraus experiments in benzene, but at significantly lower concentrations. The following conditions proved optimal, resulting in a 64% yield of **3a**: 0.1 M benzaldehyde, 0.015 M 1,4-benzoquinone, and 0.015 M benzophenone (mediator); irradiation was accomplished using a Rayonet photochemical reactor (254 nm). Use of lower benzophenone concentrations resulted in diminished yields. These results demonstrate that it is feasible to conduct this reaction at significantly lower reagent concentrations, as is needed for transfer of this chemistry to SC-CO_2 solvent.

Utilizing a view cell, the solubility of the reactants in SC-CO_2 was checked at 50°C. Generally, the solubility of polar solutes diminishes at lower CO_2 pressures.[8,9] At pressures of 1200 psi (just above the critical pressure) and at 2500 psi, benzophenone and benzaldehyde were observed to be fully soluble in SC-CO_2. However, 1,4-benzoquinone was not fully soluble, even at the higher pressure. Solubility of polar materials in SC-CO_2 can be improved either by (a) increasing the pressure (and also temperature), or (b) via the use of a co-solvent to increase the polarity of the medium.[8,9] Alcohols are frequently used as co-solvents to improve solubility of polar solutes in SC-CO_2 solvent in supercritical fluid extractions, and were tested as co-solvents for this reaction; preliminary experiments utilized benzene as a solvent (Table 1).

Use of alcohols which possess abstractable α-hydrogens as co-solvents (i.e. MeOH, EtOH, and i-PrOH) proved unsuccessful, as high yields of the reduction product (1,4-hydroquinone) were obtained at the expense of the desired coupling product. Presumably the quinone triplet state abstracts the α-hydrogen. With t-BuOH, which does not possess α-hydrogens, yields comparable to those observed in PhH were observed.

Finally, the reaction between benzaldehyde and 1,4-benzoquinone was performed in SC-CO_2 (Table 2).[10] With t-BuOH co-solvent, the yield is nearly identical to that observed in PhH (with 5% t-BuOH). The reaction could be conducted without co-solvent at high SC-CO_2 pressure, however, the yield was somewhat lower. (Presumably solubility is still the problem even at the higher pressure; this could not be confirmed because our view cell is only rated to ca. 3000 psi.)

Kraus reports that the reaction of butyraldehyde (**2b**) and benzoquinone in PhH produces the corresponding 2-acyl-1,4-hydroquinone (**3b**) in 82% yield.[1] A solubility check revealed that in SC-CO_2, butyraldehyde is soluble (0.15 M, 1200 psi and above), although the reaction product **3b** is not. Our results under dilute conditions similar to above (in PhH with 5% t-BuOH and in SC-CO_2 under various conditions) are summarized in Table 3.

The results in Table 3 demonstrate that in SC-CO_2 solvent, the product yield increases with increasing pressure. In the best case (SC-CO_2 with 5% t-BuOH), the yield is identical to that observed in PhH solvent. The effect of pressure and/or co-solvent on reaction yield suggests solubility problems at lower pressures. Indeed, visual observations reveal that the reaction mixture is only partly soluble in SC-CO_2 at low pressure, but becomes more soluble at higher pressures (or in the presence of t-BuOH).

Benzophenone has also been shown to mediate the addition of aldehydes to other α,β-unsaturated ketones. For example, Kraus reports that benzophenone-mediated reaction of acetaldehyde with 2-cyclohexen-1-one

Table 2. Benzophenone-mediated reaction of 1,4-benzoquinone with benzaldehyde in SC-CO_2

Solvent	Pressure (psi)	Time (days)	Yield **3a** (%)
SC-CO_2 + 5% t-BuOH	4672	3	49
SC-CO_2 + 5% t-BuOH	4548	2	44
SC-CO_2	6055	2	44

Table 3. Benzophenone-mediated reaction of 1,4-benzo-quinone (**1**) with butyraldehyde in SC-CO_2 and PhH (time: 2 days)
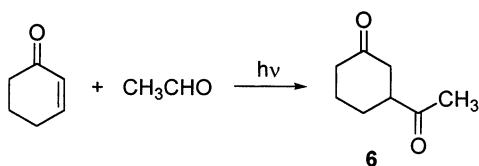
Solvent	Pressure (psi)	Yield **3b** (%)
SC-CO_2	1191	53
SC-CO_2	1492	41
SC-CO_2	1946	41
SC-CO_2	3042	50
SC-CO_2	5860	60
SC-CO_2	8180	65
SC-CO_2 + 5% *t*-BuOH	5735	81
PhH + 5% *t*-BuOH		74

Table 4. Benzophenone-mediated reaction of 2-cyclohexen-1-one with acetaldehyde

Solvent	Pressure (psi)	Time (days)	Yield **6** (%)
PhH + 5% *t*-BuOH		3	59
SC-CO_2 + 5% *t*-BuOH	6320	2	48
SC-CO_2	5730	2	30

in PhH gives 3-acetylcyclohexanone (**6**) in 40% yield (Scheme 4).[3] Our results for this reaction are summarized in Table 4. Under dilute conditions in PhH (*t*-BuOH co-solvent), the yield improves to 59%. In SC-CO_2, the yield is nearly 50% with 5% *t*-BuOH present, but drops to 30% in the absence of co-solvent (presumably because of solubility issues).

The results described herein demonstrate that SC-CO_2 is a viable replacement for benzene for the photo-induced addition of aldehydes to α,β-unsaturated carbonyl compounds. The major obstacle to overcome is related to the poor solubility of organic compounds in the non-polar SC-CO_2 solvent. However, this work demonstrates that this problem is readily solved by either (a) including an alcoholic co-solvent (specifically *t*-BuOH) to increase solvent polarity, or (b) conducting the reaction at higher CO_2 pressures (where the solubilizing power of SC-CO_2 is enhanced).

One of the limitations of this chemistry is the long reaction times, which reflect the fact that the reaction products absorb light effectively. The Kraus group is working on developing conditions that render the product insoluble so as to shorten reaction times. Thus, though the use of SC-CO_2 solvent is an important step, it is not the final step in making this reaction truly benign.

General procedure for reactions in SC-CO_2 solvent. The reactor (17 mL capacity) and apparatus for performing photochemistry in supercritical carbon dioxide was described in earlier publications.[10] In a typical procedure, to a 2 mL glass ampoule was added 1.7 mmol of aldehyde, 0.255 mmol of α,β-unsaturated ketone, and 0.255 mmol of benzophenone. In cases where a co-solvent was used, 0.85 mL was added. The ampoule was attached to a vacuum line, degassed three times by freeze–pump–thaw method, sealed under vacuum and

placed in the reactor. The reactor was then sealed and brought to 50°C. Following several argon purges to remove oxygen, the reactor was pressurized with CO_2 and allowed to equilibrate at 50°C and the desired pressure for 30 minutes. (Note: During pressurization, the glass ampoule ruptures.) A Pyrex® filter was placed on the reactor, and the reaction mixture was irradiated with a 150 W Xenon arc lamp for 2–3 days. Following illumination, the contents of the reactor were bubbled slowly into 12 mL of ethyl acetate cooled to 0°C. After depressurization, the reactor was washed with ethyl acetate and the combined washing analyzed by GC (after addition of phenyl ether as an internal standard).

Note: Because of the hazards associated with high pressure work, we were especially careful to ensure that the pressures utilized in this study did not exceed the specifications of our system (ca. 15,000 psi).

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Scheme 4.

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