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Benzophenone-Mediated Conjugate Additions of Aromatic Aldehydes to Quinones

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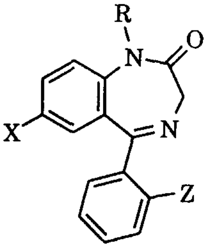
Key Words: quinone; photochemistry; benzophenone; radical

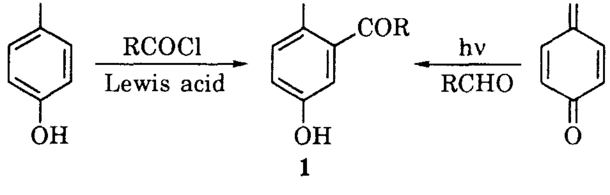
Abstract: *Benzophenone increases the efficiency of the photochemically mediated addition of aldehydes to quinones.*

Diaryl ketones are valuable as intermediates for the synthesis of pharmaceuticals such as diazepam (Valium).[1] They are also important as monomers for the synthesis of novel thermostable polymeric materials.[2]



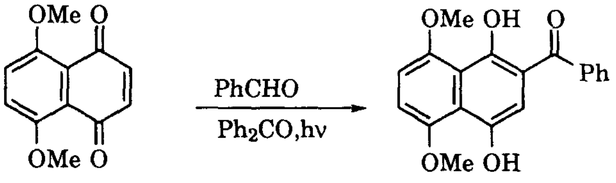
X=Cl, R=Me, Z=H Diazepam
X=NO_2, R=H, Z=Cl Clonazepam
X=Cl, R=Me, Z=F Fludiazepam

They are generally prepared by way of Friedel-Crafts reactions.[3] The yields obtained by the Friedel-Crafts procedure are usually good, but the toxic byproducts generated in this reaction have prompted increasing interest in the development of alternative, more environmentally benign pathways. We recently reported a study of the photochemical addition of aliphatic aldehydes and benzaldehyde to benzoquinone and naphthoquinone.[4] These reactions, which can be conducted using visible light, proceeded in very good yields on multigram scales with essentially no byproducts. This reaction also exemplifies the principle of atom economy, wherein all of the



atoms in the starting materials become incorporated into the product.[5]

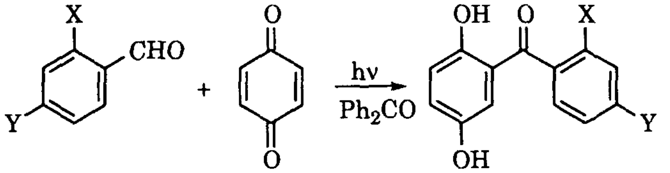
In this reaction the excited state of the quinone abstracts a hydrogen atom from the aldehyde. Radical coupling followed by tautomerization leads to the hydroquinone product. We recently found that this photochemical reaction of benzaldehyde with 5,8-dimethoxynaphthoquinone failed to provide ketone **2**.



2

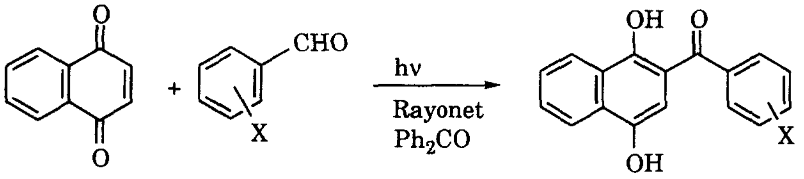
Since quinones are known to react efficiently with alkyl radicals[6], we employed benzophenone and irradiated at a wavelength where benzophenone would selectively absorb the light. The triplet excited state of benzophenone was expected to generate an acyl radical by hydrogen atom abstraction, with the idea that the acyl radical would then add to the quinone. The resulting radical would react with the benzhydrol radical to regenerate benzophenone. Using a catalytic amount of benzophenone, a 61% yield of adduct **2** was obtained. We next compared the effect of added benzophenone on the photochemically-mediated additions of ortho- and para-substituted aromatic aldehydes with benzoquinone. The results are depicted below. The presence of benzophenone led to an increase of 15-20% in the isolated yields when compared to the isolated yields from reactions performed in the absence of benzophenone.

Table 1. Benzophenone-Mediated Additions to Benzoquinone



Entry	X	Y	% Yield
1	Cl	H	78
2	OCH_3	H	72
3	CH_3	H	65
4	CO_2Me	H	58
5	H	OCH_3	77
6	H	Cl	73
7	H	CH_3	79
8	H	CHO	42
9	H	F	61

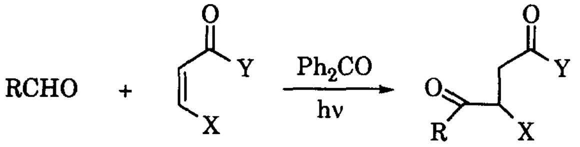
The reaction of ortho-substituted aldehydes is relevant, since many compounds related to diazepam (e,g. fludiazepam[7]) have ortho-substituted aryl subunits. The presence of ortho substituents such as methyl and methoxyl groups raises the question of whether radical translocation[8] might occur. There is some precedent for intramolecular hydrogen atom transfers in aromatic ring systems.[9] Based on the results in Table 1, radical translocation does not appear to be a problem. The reaction of naphthoquinone with ortho- and para-substituted benzaldehydes is shown below.[11]

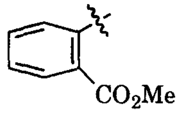


X = o-Cl 60.4%
X = o-F 68.0%
X = o-Me 57.0%
X = p-Me 70.0%
X = p-Cl 65.0%

In a classic study in synthetic photochemistry, Fraser-Reid and coworkers employed benzophenone to catalyze the conjugate addition of simple alcohols and acetals to unsaturated ketones.[10] In order to determine whether the acyl radicals[12] generated using benzophenone would react with enones, we examined the reaction of benzaldehyde with cyclohexenone. This reaction produced a 69% yield of 3-benzoylcyclohexanone.

Table 2. Benzophenone-Mediated Conjugate Additions of Aldehydes



Entry	R	X Y	% Yield
1	Ph	$-CH_2CH_2CH_2-$	69
2	CH_3	$-CH_2CH_2CH_2-$	40
3	Pr	$-CH_2CH_2CH_2-$	46
4		$-CH_2CH_2CH_2-$	39
5	Ph	H OMe	15
6	Ph	H CH_3	30
7	PhCH=CH	$-CH_2CH_2CH_2-$	40

Similarly, the reaction of cyclohexenone with acetaldehyde, butyraldehyde and cinnamaldehyde also generated adducts. Reactions of benzaldehyde with methyl vinyl ketone and methyl acrylate were also examined. Although the most of the yields are modest, this preparation of 1,4-diketones is both direct and operationally convenient.

The use of benzophenone to promote the photochemically mediated additions of aromatic aldehydes to quinones both extends the scope of this reaction and improves the yields. The combination of benzophenone and light can also be used to promote addition of aliphatic and aromatic aldehydes to cyclohexenone and other Michael acceptors.

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11. General Procedure for the photochemical addition of aldehydes to quinones: Benzoquinone (4.80 g, 44.4 mmol) and the freshly distilled aldehyde (20 mL, 346.7 mmol) and benzophenone (2.5 mmol) were dissolved in dry benzene (240 mL) and the solution was degassed with nitrogen for 15 min. The solution was irradiated with a high-pressure mercury vapor lamp with a Pyrex filter for 5 days. The solution was concentrated in vacuo and the residue was purified by silica gel chromatography using a mixture of hexanes:ethyl acetate to afford the desired products. 2: 300 MHz NMR ($CDCl_3$) δ 3.97 (s, 6H), 6.81 (s, 2H), 7.35-7.53 (m, 3H), 7.85-7.93 (m, 2H), 9.45 (s, 1H). IR ($CDCl_3$) 3450, 1696, 1616, 1110, 908, 733 cm^{-1}. 300 MHz NMR ($CDCl_3$) δ 56.6, 105.9, 109.2, 117.2, 128.2, 129.6, 132.8, 138.3, 145.1, 151.4, 196.2. MS (C I, NH_3 gas) m/z 105, 325 (M+1).
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