2-Benzoylbenzoic Acid: A Photolabile Mask for Alcohols and Thiols

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Received August 23, 1996[⊗]

Photolysis of 2-benzoylbenzoate esters of primary and secondary alcohols **1** in the presence of a hydrogen donor (2-isopropanol) or an electron donor (primary amines) produces the corresponding alcohol in high yield. The fate of the benzoate is dependent on the conditions used for the photoreaction. In 2-propanol, the ketyl radical that derives from photoreduction dimerizes, to afford the benzpinacol product 3,3′-diphenylbiphthalidyl, **5**. In the presence of amines the product is 3-phenylphthalide, **6**, a benzhydrol derivative which is the result of simple reduction of the ketone followed by lactonization. While the photoproduct of the benzoate−2-propanol reaction results from anticipated free radical chemistry, the amine-promoted reaction appears to result from a second, "dark", electron transfer process. We conclude that 2-benzoylbenzoic acid is an effective photolabile protecting group for primary and secondary alcohols, and preliminary studies indicate that thiols can be protected in an analogous way. Studies on the effect of benzophenone substituents and reaction solvent on the benzhydrol:benzpinacol product ratio provide mechanistic insight into the process.

The use of photoremovable protecting groups has shown a marked increase in recent years. Thus, photoremovable protecting groups have recently seen new uses to "cage" enzymes by protecting alcohol and amine groups. Nucleophilic functional groups have also been protected by photoremovable groups in recent applications in peptide and nucleic acid syntheses. The most popular strategies for functional group protection by photoremovable groups involve the use of the 2-nitrobenzyl,[2,3] substituted benzyloxycarbonyl,[4−6] phenacyl,[7] and 3,5-dimethoxybenzoinyl groups.[8,9] These functional groups have found widespread use in protecting both alcohols and amines in organic synthesis. While the mechanism for photodeprotection is still under active investigation in some cases for these established photoprotecting groups, the critical photochemical step involves either intramolecular H transfer (2-nitrobenzyl and analogs) or carbon−heteroatom bond fragmentation (benzyloxycarbonyl, phenacyl, benzoinyl). More recently developed photoprotecting groups depend upon *trans*−*cis* isomerization as the critical photochemical step.[10−12] In one case photochemical *trans*−*cis* isomerization is coupled to ground-state lactonization and release of an enzyme alcohol functional group, thus producing the native active enzyme and opening the enzyme "cage".

In order to expand the repertoire of photochemical reactions used in functional group protection, we have sought to develop strategies based upon the familiar photoreduction of the phenone functional group. In considering various possibilities, we were led to the conclusion that esters of 2-benzoylbenzoic acid might be effective photolabile masks for alcohol functionalities. Indeed, there are reports in the literature of the reduction of 2-benzoylbenzoate esters **1** through chemical,[13] polarographic,[14,15] and photochemical[16] means, which give as product either 3-phenylphthalide, **6**, or its dimer **5** (Scheme 1). These reactions also result in the production of the alcohol from the ester precursor although previous work has focused on the fate of the aromatic product. On the basis of these reports, we sought to characterize the utility of these esters as photolabile masks for the alcohol group. This report describes the synthesis of several esters of 2-benzoylbenzoic acid and the study of the photoreduction of these esters using both H atom donors and electron transfer donors as the reducing agent.

Results

Primary and secondary alcohols and one thiol were protected as the corresponding 2-benzoylbenzoate ester. Efforts to make an ester using a tertiary alcohol (1-methyl-1-phenylethanol) failed. The synthesis of these esters was carried out by DCC coupling of the alcohol (or thiol) and commercially available 2-benzoylbenzoic acid in pyridine. Yields of isolated ester were in the range of 50−79%.

Photoreduction of these compounds was carried out using a 450 W medium pressure mercury lamp. The solutions were degassed by bubbling argon through them

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[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

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S0022-3263(96)01638-6 CCC: $12.00

Scheme 1

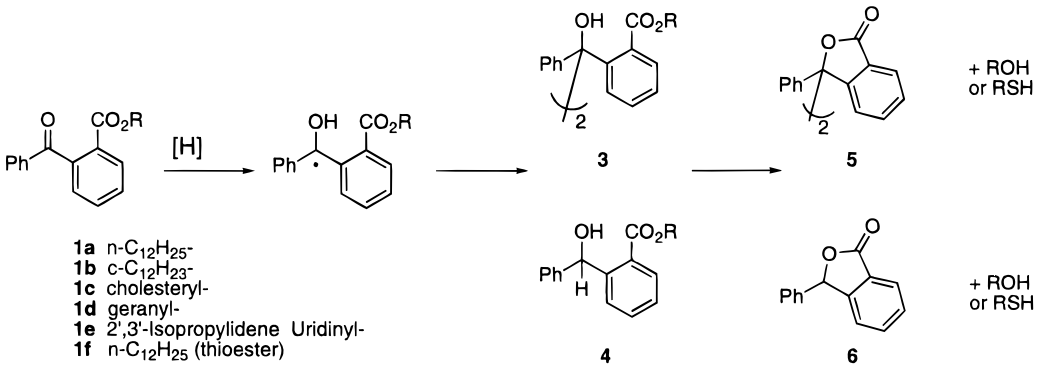

Table 1. Photoreduction of Benzoylbenzoate Esters with 2-Propanol or Primary Amines

			yields[b] (%)			
entry	substrate	conditions[a]	ROH(SH)	RSSR	**5**	**6**
1	**1a**	a, 5 h	95		0	95
2	**1a**	b, 5 h	95		95	0
3	**1b**	a, 18 h	85		0	80
4	**1b**	b, 18 h	85		85	tr
5	**1c**	a, 18 h	100		0	95
6	**1c**	b, 18 h	20		5	0
7	**1d**	a, 5 h	85		0	80
8	**1d**	c, 5 h	90		0	70
9	**1e**	c, 5 h	60		0	75
10	**1e**	d, 24 h	90		0	80
11	**1f**	a, 5 h	60	20	>45	20

[a] a: 0.1 M ketone, 1 M cyclohexylamine, 1:1 benzene:acetonitrile, Pyrex filter. b: 0.01 M ketone, 1:1benzene:-2-propanol, Pyrex filter. c: 0.1 M ketone, 1 M *sec*-butylamine, 1:1 benzene:-2-propanol, Pyrex filter. d: 0.1 M ketone, 1 M *sec*-butylamine, 1:1 benzene:acetonitrile, uranium filter. [b] Yield determined by NMR.

for 20 min and were cooled during the photolysis with a circulating water bath. A Pyrex filter was used in most cases although photolysis through a uranium glass filter also was effective, *vide infra*. Reaction times varied from 5 to 24 h. The yields listed in Table 1 were calculated from ^{1}H NMR of the crude reaction mixture using an internal standard. Products of the photolysis were also isolated and characterized or compared to authentic samples. Photoreductions of **1a**,**b** by benzene/2-propanol (entries 2 and 4, Table 1) gave good yields of alcohol and diphthalidyl **5**, obtained as a mixture of *dl* and *meso* forms in approximately equal amounts. Benzene was used as a cosolvent due to the low solubility of the keto esters in neat 2-propanol. Dimer **5** precipitated from solution during the course of the reaction.

Photoreduction of **1c** gave a poor yield of cholesterol and **5** using 2-propanol as the H donor. However, the photoreduction of **1a**−**e** using cyclohexylamine as the reducing agent gives alcohol in excellent yield in all cases examined. The byproduct of the amine-mediated photoreaction is not diphthalidyl **5** but 3-phenylphthalide, **6**. Spectrometric (NMR) and chromatographic (GC, TLC) analysis indicated that the only products of the photoreduction of keto esters **1a**−**e** are the alcohol and **6** after aqueous workup and the removal of volatile products *in vacuo*. Prior to removal of volatile materials, GC and TLC indicated that cyclohexanone, presumably formed by hydrolysis of cyclohexylimine during aqueous workup, was also formed in the reaction. The reaction of **1a** was followed by GC and found to be complete in 5 h. Reactions of the other esters of primary alcohols studied were also found to be complete in 5 h as well. However, reaction of the esters of secondary alcohols required 18 h of photolysis.

In the case of **1a**, dodecanol was isolated in 90% yield by flash chromatography, while the isolated yield of **6** in this experiment was 74%. The reducing agent may be an amine other than cyclohexylamine, as shown in entries 8−10 where *sec*-butylamine was used. Protected nucleoside **1e** was photoreduced with *sec*-butylamine and a uranium glass filter (λ_{cutoff} < 350 nm) (entry 10). The yield of nucleoside, as determined by NMR, was 90% and that of 3-phenylphthalide (**6**) was 80%. Photolysis of **1e** in the absence of the uranium glass filter gave a significantly lower yield of alcohol, as well as unidentified side products, but about the same yield of **6** (entry 9). This is, presumably, due to photochemistry involving the aromatic ring of the nucleoside which has an absorbance at wavelengths up to 330 nm. The use of the uranium glass filter also demonstrates that the masking group can be removed with light of λ = 366 nm, though a longer photolysis time is required. The keto esters are transparent at wavelengths greater than 390 nm (data not shown).

The photoreduction of thio ester **1f** using cyclohexylamine as the reducing agent gave a mixture of dodecanethiol and dodecane disulfide, which were produced in a 3:1 ratio. In addition, both 3-phenylphthalide, **6**, and diphthalidyl **5** were produced in a 2:1 ratio. Photolysis of the thio ester in the absence of cyclohexylamine produced significant quantities of diphthalidyl **5** and dodecane disulfide. When the disulfide was photolyzed in the presence of cyclohexylamine, it was slowly converted to thiol. Additional reaction pathways afford a more complex reaction mixture in the thio ester photolysis than the cases involving oxo esters.

Cyclohexylamine-*N*-d_2 was prepared by the method of Cohen.[17] Photoreduction of **1g** with cyclohexylamine-*N*-d_2 afforded 3-phenyl phthalide-*3*-*d*, **6**, in 92% yield (Scheme 2). Photolysis of **1g** in benzene:acetonitrile but with 10 equiv of 2-propanol instead of cyclohexylamine produces **5** instead of **6** (Scheme 2). The phthalide dimer **5** was suspended in 1:1 C_6D_6:CD_3CN with 10 equiv of cyclohexylamine, and this mixture was followed by NMR for 48 h. At the end of this period no change in the NMR was observed.

The set of benzophenones shown in Table 2 was photoreduced using cyclohexylamine in 1:1 benzene: acetonitrile to test the effect of substituents on the photoreaction. The products of the reactions listed in Table 2 were determined by ^{1}H NMR and MS. For the

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Scheme 2

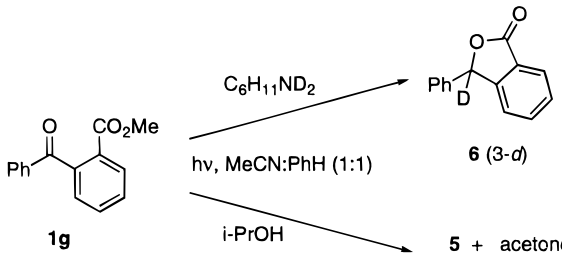


Table 2. Cyclohexylamine Photoreduction Products from Benzophenones

compd	Ar	Ar′	8	9
7a[a]	2-(MeO)C_6H_4	2-(CO_2Me)C_6H_4	>95[b]	<5
7b[a]	2,5-(MeO)$_2C_6H_3$	2-(CO_2Me)C_6H_4	>95	<5
7c	4-(MeO)C_6H_4	Ph	<5	>95
7d	4-(MeO)C_6H_4	4-(MeO)C_6H_4	<5	>95
7e	4-(Cl)C_6H_4	4-(Cl)C_6H_4	90	10
7f	4-(CO_2Me)C_6H_4	Ph	>95	<5
7g	3-(CO_2Me)C_6H_4	Ph	70	30
1g[a]	2-(CO_2Me)C_6H_4	Ph	>95	<5
7h	3-(NO_2)C_6H_4	Ph	<5	>95
7i	4-(NO_2)C_6H_4	Ph	*c*	
7j	Ph	Ph	<5	>95
7k	4-MePh	4-MePh	10	90

[a] The product obtained was the corresponding lactone. [b] >95 indicates only one product observed by NMR. [c] Complex mixture.

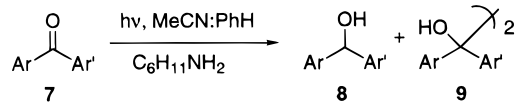
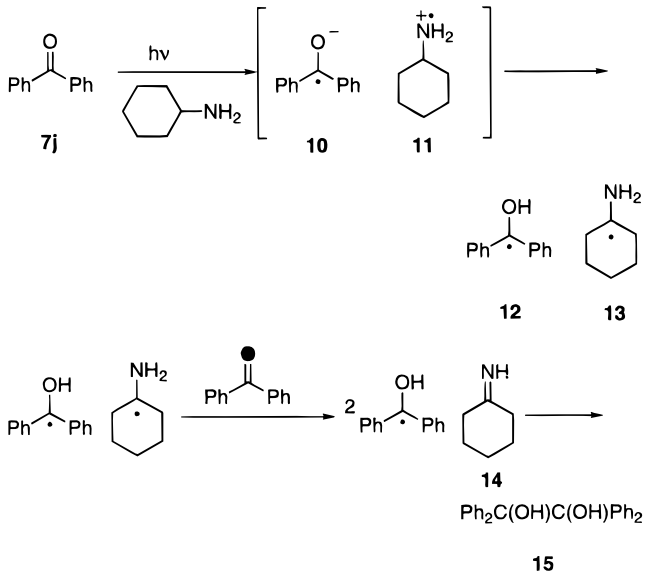


Figure 1. Photoreduction of substituted benzophenones with cyclohexylamine.

most part the trend holds that benzophenones with an electron-withdrawing group *ortho* or *para* to the ketone (**7a**,**b**,**f**,**g**) react to give reduction to benzhydrol. Those benzophenones that do not have such a substituent (**7c**,**d**,**h**,**j**,**k**) react to give pinacol coupling products. Ketone **7g** gave significant amounts of both benzhydrol and pinacol products. While the carboxyl in this compound (**7g**) is not in conjugation with the ketone, it does make the ring electron deficient. 4-Nitrobenzophenone, **7i**, gave a complex mixture of products, a result that may be due to photochemistry directly involving the nitro substituent. Two of the benzophenones studied, **7a**,**b**, have the possibility of reacting via abstraction of the δ-hydrogens on the *ortho* methoxy substituent.[18,19] This is not observed under the photoreduction reaction conditions. When **7a** or **7b** is photolyzed in dry benzene and the reaction followed by NMR, little reaction occurs. The sample is degraded over 48 h, and the solution becomes yellow. However, in the case of **7a**, some signals appear that are consistent with the expected spirolactone. It is not surprising that δ-hydrogen abstraction is not observed in the presence of an electron or H atom donor as reactions of these reducing agents with excited ketones are fast relative to the abstraction of δ-hydrogens.[18b]

The solvent dependence of the photoreduction of 4,4′-dimethylbenzophenone, **7k**, with cyclohexylamine was also studied. In benzene the ratio of benzhydrol, **8k**, to

Scheme 3



benzpinacol, **9k**, is 1:20. In 1:1 benzene:acetonitrile, the product ratio of **8k:9k** is 1:5. In wet acetonitrile there is slightly more benzhydrol produced, the product ratio being 1:4, but in formamide and DMSO the ratio of **8k:9k** is 1:1 and 4:3, respectively.

Discussion

The experiments reported here suggest that 2-benzoylbenzoate esters are effective protecting groups for alcohols. Photoreduction proves to be efficient under conditions where a good H atom donor (2-propanol) or electron donor (amine) is present. It is clear that the photoreduction of ketones **1a**−**e** using amine-reducing agents produces the benzhydrol analog **6** in an apparent 2-electron reduction, instead of the expected benzpinacol **5**, produced by 1-electron reduction of the ketone. The possibility that this is caused by a dark reaction between **5** and the amine base is ruled out by the experiment in which no change is observed in **5** after 2 days in the presence of cyclohexylamine under the reaction conditions. Cohen reports that the photoreduction of benzophenone with cyclohexylamine in benzene affords nearly quantitative yields of benzpinacol, **15** (Scheme 3),[17] and it was our expectation that 2-benzoyl benzoate esters would have similar chemistry when photoreduced. The Cohen mechanism for formation of pinacol following reduction with a primary amine is shown in Scheme 3. Following the formation of a polar exciplex between the amine and ketone, a proton transfer occurs to yield the radical pair **12** and **13**. Hydrogen atom transfer from **13** to ground-state phenone produces a second benzhydryl radical, and coupling of two of these radicals gives the pinacol **15**.[17,20−26]

A mechanism consistent with our observations of the photoreactions of substituted benzophenones is presented in Scheme 4. The **2**−**13** radical pair is formed after exciplex formation and proton transfer. These steps are in accord with the initial steps of the mechanism proposed for photoreduction of benzophenone by aliphatic amines.[17,20−26] The ketyl radical center for **2** is in direct

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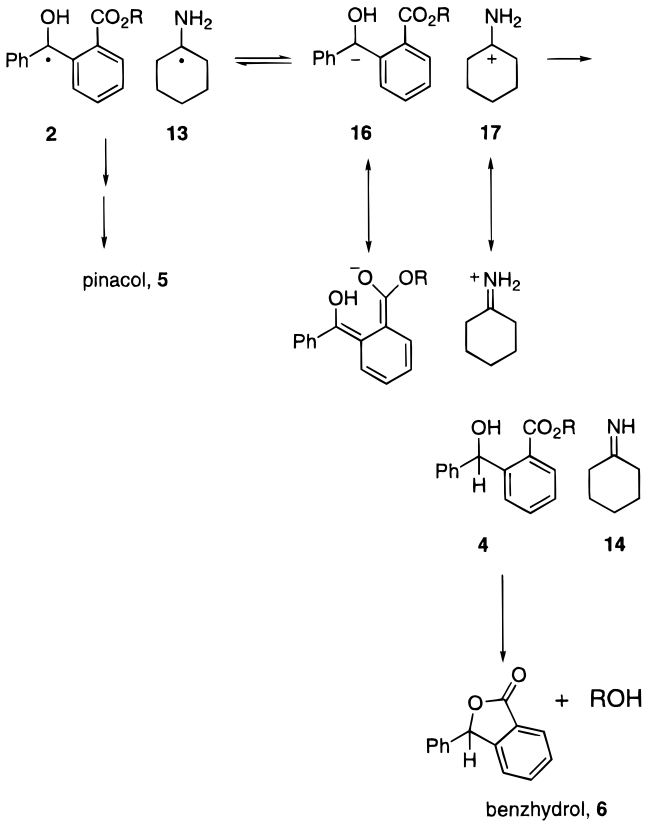
Scheme 4



conjugation with the *ortho* carboxyl group. The electron-withdrawing character of the carboxyl group should increase the ability of the radical to accept an electron, lowering its reduction potential. Electron transfer from the easily oxidized α-amino radical **13** gives carbanion **16** and iminium ion **17**. Protonation of **16** by **17** gives the products in a manner that is consistent with the deuterium-labeling studies shown in Scheme 2.

Electrochemical studies have shown that α-amino radicals, such as **13**, are easily and quickly oxidized to the iminium ion.[27,28] Polaragraphic data also demonstrate that ketyl radicals are reduced easier than the corresponding ketone.[14] Pac and Peters have, in fact, both reported electron transfer from carbon-centered radicals in conjugation with nitrogen lone pairs to ketyl radicals. Peters has observed the hydroxydiphenylmethane anion by flash photolysis in the photoreduction of benzophenone using *N*-methylacridan as the reducing agent.[29] Pac has shown that the fate of the intermediate ketyl radical is dependent on whether or not electron-withdrawing groups are conjugated to the radical center.[30−34] As an example, the $Ru(bpy)_3$-sensitized photoreduction of the dipyridyl ketone gives the corresponding benzhydrol almost exclusively.[32] Less electron poor ketones give pinacols and radical coupling products. The same effect is observed in the photochemical reduction of olefins[33] in cases using triethylamine[30] as the reducing agent. Pac's suggestion is that electron-withdrawing groups conjugated to the ketone lower the reduction potential of the ketyl radical to the point that it can be reduced by the pyridinal radical. In the absence of an electron-withdrawing group, the reduction potential of the ketyl radical is too high for the electron transfer to be energetically feasible. Whitten has also suggested a double electron transfer mechanism in the photoreduction of anthraquinone with amine donors.[35] The second electron transfer results in an anthrahydroquinone/iminium ion pair in equilibrium with an anthrahydroquinone/α-amino radical pair. The position of this equilibrium is solvent dependent. The solvent dependence of radical pair/ion pair equilibria has also been elegantly demonstrated by Arnett.[36−38]

Another possibility for the formation of benzhydrol/imine products **6** and **14** is one involving disproportionation of the **2**−**13** radical pair. It is unclear why the **2**−**13** pair would disproportionate while the **12**−**13** pair does not, but polar effects in the transition state may play a role.[39]

If either direct charge transfer or a polar effect in disproportionation operate, any benzophenone with an electron-withdrawing group conjugated to the ketone should give benzhydrol when photoreduced using an amine-reducing agent. This is precisely what we observe in the photoreactions of the series of benzophenones presented in Table 2. Those phenones that have electron-withdrawing groups substituted *ortho* or *para* to the carbonyl give benzhydrol product, presumably from an intermediate ion pair or polar transition state. Further evidence for these mechanisms is found in the solvent dependence of the photoreduction of 4,4′-dimethylbenzophenone with cyclohexylamine. Polar solvents that stabilize polar intermediates provide more benzhydrol, while amine-promoted photoreduction of this benzophenone in nonpolar solvent gives the pinacol product. Clearly the substituent and solvent effects on product

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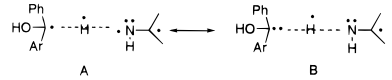
(39) A and B are two resonance structures for the disproportionation transitions state of radical pairs **2**−**13** and **12**−**13**. In the case of **2**−**13** the electron-withdrawing character of Ar will increase the contribution from structure B relative to its contribution in **12**−**13**. The decrease in energy of the overall transition state due to a polar contribution may explain why **2**−**13** appears to disproportionate while **12**−**13** does not.



distribution reflect some amount of charge transfer in the steps leading to benzhydrol.

The results obtained with thio ester **1f** are more complex than those in the cases of oxo esters **1a**−**e**. The reduction of the ketone undoubtedly leads to thiol and either **5** or **6** as in the cases of the oxo esters. Additionally, our experiments show that, under the reaction conditions, photolysis of **1f** in the absence of reducing agent leads to **5** and the corresponding disulfide. The disulfide can react under these conditions to give thiol. All of these reactions are, most likely, occurring simultaneously, leading to the observed mixture of products.

The question of when lactonization actually occurs is not addressed by any of these experiments, and it should be noted that it is possible that lactonization could occur at several steps in the reaction sequence. The ketyl radical anion (analogous to **10**) may lactonize to afford an alkoxide anion and the 3-phenylphthalidyl radical. Alternatively, the ketyl radical may cyclize to give the alcohol and 3-phenylphthalidyl radical, or lactonization may not occur until the benzhydrol has been formed, as shown in Scheme 4.

We conclude that *o*-benzoylbenzoate esters serve as photolabile protecting groups for alcohols. Primary and secondary alcohols as well as thiols can be easily masked by the formation of the corresponding 2-benzoylbenzoate esters using very inexpensive reagents. These esters can be converted in high yield to the alcohol/thiol and 3-phenylphthalide (**6**), under electron transfer conditions, or its dimer (**5**), in the presence of hydrogen donors.

Experimental Section

Materials and Methods. Melting points are uncorrected. The following chemicals were obtained from commercial sources and used as received: 2-benzoylbenzoic acid, 3-benzoylbenzoic acid, 4-benzoylbenzoic acid, DCC, pyridine, 1-dodecanol, cyclododecanol, cholesterol, geraniol, 2′,3′-isopropylideneuridine, 1-dodecanethiol, cyclohexylamine, *sec*-butylamine, 4-methoxybenzophenone, 4,4′-dimethoxybenzophenone, 4,4′-dichlorobenzophenone, 3-nitrobenzophenone, 4-nitrobenzophenone, benzophenone, 4,4′-dimethylbenzophenone, dimethoxybenzene, trifluoroacetic anhydride, monomethyl phthalate, and 2-bromoanisole. Methyl 2-benzoylbenzoate,[13] methyl 3-benzoylbenzoate,[40] methyl 4-benzoylbenzoate,[35] 3-phenylphthalide,[13] and 3,3′-diphenylbiphthalidyl[41] were prepared by literature methods. Reactions were run in flame-dried glassware under argon. Gas chromatography was performed with flame ionization detection, coupled to a digital integrator (15 m SPB-5, 0.20 mm i.d.). Photolyses were carried out with a 450 W medium pressure mercury lamp. Mass spectra were obtained using methane/ammonia (2×10^{-4} atm) for chemical ionization mass spectra.

General Procedure for the Protection of Alcohols and Thiols. To a solution of 2-benzoylbenzoic acid (2.26 g, 10 mmol), alcohol or thiol (0.9 equiv, 9 mmol), and DMAP (0.244 g, 2 mmol) in pyridine (15 mL) was added DCC (2.06 g, 10 mmol) in one portion. The reaction mixture was stirred at 25 °C under argon for 48 h. The reaction mixture was partitioned between 1 M HCl (200 mL) and EtOAc (200 mL). The layers were separated, and the aqueous layer was extracted with 1 × 150 mL of EtOAc. The combined organic layers were washed with 1 × 200 mL of 1 M HCl and 1 × 100 mL of brine; dried ($MgSO_4$), and concentrated *in vacuo*. The desired product was isolated via column chromatography (SiO_2, hexane/EtOAc) (Table 3).

(40) Wagner, P. J.; Siebert, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 7329−7335.

(41) Bhatt, M. V.; Kamath, K. M.; Ravindranathan, M. *J. Chem. Soc.* **1971**, 3344−3347.

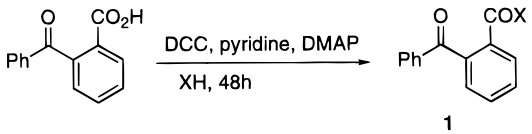


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Figure 2. Synthesis of benzoylbenzoate esters, **1a**−**e** and thio ester **1f**.

Table 3. Isolated Yields of Benzoylbenzoate Esters 1a−f

XH	product	yield (%)
n-$C_{12}H_{25}OH$	**1a**	76
c-$C_{12}H_{23}OH$	**1b**	50
cholesterol	**1c**	67
geraniol	**1d**	63
2′,3′-isopropylideneuridine	**1e**	79
n-$C_{12}H_{25}SH$	**1f**	76

Dodecyl 2-benzoylbenzoate (1a): yield 2.68 g (6.8 mmol, 76%); obtained as a colorless oil via flash column chromatography (SiO_2, 9:1 hexane:EtOAc); IR (CCl_4) 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 8.09 (d, 1H, J = 10 Hz), 7.80 (d, 2H, J = 10 Hz), 7.60 (m, 3H), 7.45 (m, 3H), 4.01 (t, 2H, J = 7.5 Hz), 1.2 (m, 20H), 0.85 (t, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, ppm) 196.9, 165.9, 141.6, 137.0, 133.0, 132.2, 130.1, 129.5, 129.4, 128.4, 127.6, 65.7, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.1, 25.8, 22.7, 14.1; GC/CIMS (CH_4/NH_3(g)) m/z 395 (MH^+). Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.00; H, 8.79.

Cyclododecanyl 2-benzoylbenzoate (1b): yield 1.77 g (4.52 mmol, 50%); obtained as a white solid (SiO_2, 7:1 hexane:EtOAc); mp 102−103 °C; IR (Nujol) 1710, 1669 cm^{-1}; ^1H NMR ($CHCl_3$, ppm) 8.08 (dd, 1H, J = 1.2, 7.7 Hz), 7.77 (m, 2H), 7.58 (m, 3H), 7.43 (d, 1H, J = 7.7 Hz), 7.37 (m, 2H), 5.00 (m, 1H), 1.40 (m, 4H), 1.22 (m, 18H); ^{13}C NMR ($CHCl_3$, ppm) 196.7, 165.3, 141.4, 137.1, 133.1, 132.3, 130.3, 129.7, 129.5, 129.1, 128.5, 128.2, 127.2, 74.3, 28.2, 24.1, 24.0, 23.1, 23.0, 20.4; MS/FAB m/z 393.25 (MH^+). Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.68; H, 8.17.

Cholesteryl 2-benzoylbenzoate (1c): yield 3.60 g (6.1 mmol, 67%); obtained as a white solid via flash column chromatography (SiO_2, 9:1 hexane:EtOAc); mp 119−119.5 °C; IR (Nujol) 1719, 1673 cm^{-1}; ^1H NMR ($CHCl_3$, ppm) 8.10 (dd, 1H, J = 1.26, 7.74 Hz), 7.78 (m, 2H), 7.60 (m, 3H), 7.41 (m, 3H), 5.26 (m, 1H), 4.59 (m, 1H), 0.94−2.08 (m, 30H), 0.88 (m, 12H), 0.66 (s, 3H); ^{13}C NMR ($CHCl_3$, ppm) 196.84, 165.06, 141.47, 139.28, 137.21, 133.11, 132.32, 130.23, 129.47, 129.41, 129.34, 128.47, 127.48, 122.65, 75.54, 56.56, 56.04, 49.84, 42.23, 42.20, 39.62, 39.46, 37.17, 36.73, 36.47, 36.12, 35.74, 34.89, 31.80, 31.74, 28.18, 27.98, 26.89, 25.41, 24.22, 23.79, 22.81, 22.54, 20.92, 19.18, 19.14, 18.67, 11.82, 11.76; MS/FAB m/z 595.18 (MH^+). Anal. Calcd for $C_{40}H_{54}O_3$: C, 82.78; H, 9.15. Found: C, 82.67; H, 9.23.

Geranyl 2-benzoylbenzoate (1d): yield 2.3 g, (6.35 mmol, 63%); obtained as a colorless oil via flash column chromatography (SiO_2, 6:1 hexane:EtOAc); IR (neat) 3062, 2964, 2854, 2118, 1720, 1675, 1597, 1581 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 8.06 (d, 1H, J = 6.4 Hz), 7.74 (d, 2H, J = 7.2 Hz), 7.56 (m, 3H), 7.42 (m, 3H), 5.07 (m, 2H), 4.53 (d, 2H, J = 8.5 Hz), 1.97 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 142.6, 141.6, 133.0, 132.3, 131.8, 130.1, 129.5, 129.4, 128.3, 127.6, 123.7, 118.0, 117.4, 62.3, 39.4, 36.1, 33.7, 27.0, 26.2, 25.6, 24.8, 17.7, 16.3; MS/FAB m/z 363.3 (MH^+). Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.26; H, 7.33.

5′-((2-Benzoyl)benzoyl)-2′,3′-isopropylideneuridine (1e): yield 3.5 g (7.11 mmol, 79%); obtained as a white solid via flash column chromatography (SiO_2, 1:1 EtOAc:hexane); mp 90−93 °C; IR (Nujol) 1717, 1676, 1671, 1595, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 8.17 (brs, 1H), 8.03 (dd, 1H, J = 1.2, 7.6 Hz), 7.76 (d, 2H, J = 6.8 Hz), 7.62 (m, 3H), 7.43 (m, 3H), 7.23 (t, 1H, J = 8.0 Hz), 5.67 (d, 1H, J = 2.4 Hz), 5.59 (dd, 1H, J = 2.4, 8.0 Hz), 4.80 (m, 1H), 4.62 (m, 1H), 4.41 (q, 1H, J = 8.8 Hz), 4.21 (m, 2H), 1.54 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 203.8, 194.7, 178.4, 174.8, 162.4, 149.6, 141.4, 136.7,

133.4, 132.6, 130.3, 129.9, 129.5, 128.6, 128.0, 114.8, 102.5, 93.3, 84.3, 80.5, 64.5, 27.0, 25.2; MS/FAB *m/z* 493.2 (MH^+). Anal. Calcd for $C_{26}H_{24}O_8N_2$: C, 63.41; H, 4.91; N, 5.69. Found: C, 63.01; H, 5.30; N, 5.67.

Dodecyl 2-benzoylbenzenethioate (1f): yield 2.68 g (6.8 mmol, 76%); obtained as a colorless oil via flash chromatography (SiO_2, 9:1 hexane:EtOAc); IR (neat) 3061, 2924, 2852, 1777, 1669, 1597 cm^{-1}; ^1H NMR ($CHCl_3$, ppm) 7.98 (dd, 1H, J = 1.33, 7.53 Hz) 7.75 (m, 2H), 7.58 (m, 3H), 7.41 (m, 3H), 2.86 (t, 2H, J = 7.27 Hz), 1.43 (m, 2H), 1.26 (m, 17H), 0.88 (t, 3H, J = 6.72 Hz); ^{13}C NMR ($CHCl_3$, ppm) 196.9, 192.1, 139.2, 137.2, 136.9, 132.9, 129.8, 129.4, 128.3, 128.2, 128.1, 34.9, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.7, 22.6, 14.1; MS/FAB *m/z* 411.38 (MH^+). Anal. Calcd for $C_{26}H_{34}O_2S$: C, 76.05; H, 8.35; S, 7.81. Found: C, 76.10; H, 8.41; S, 7.73.

Methyl 2-(2-Methoxybenzoyl)benzoate (7a). One-fourth of a 200 mL solution of 2-bromoanisole (7.5 g, 40 mmol) in THF was added to magnesium turnings (1.05 g, 42 mmol) which had been ground and dried under high vacuum. When the THF began to reflux the remainder of the solution was added dropwise so that reflux was maintained. Once addition was complete the solution was heated to reflux with a heating mantle. Heating was maintained for 16 h. The yellow solution was allowed to cool to ambient temperature and then cooled further to −78 °C with a dry ice/acetone bath. The solution remained homogeneous throughout this process. A solution of monomethylphthaloyl chloride (from monomethyl phthalate and thionyl chloride) in THF (0.27 M, 150 mL) was added dropwise over 45 min. The resulting mixture was maintained at −78 °C for 1 h and then allowed to warm to ambient temperature with the cold bath. After 7 h the reaction mixture was poured into 300 mL of 1 N HCl/ice and 300 mL of EtOAc. This mixture was stirred for 15 min, and the layers were separated. The aqueous layer was extracted once more with 100 mL of EtOAc, and the combined organic layers were washed with 3 × 200 mL of saturated sodium bicarbonate, 1 × 200 mL of 1 N HCl, and 1 × 300 mL of brine. The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield a viscous yellow oil (11.01 g). The oil was dissolved in a small amount of ether, and hexane was added until a precipitate had formed. This solid was recrystallized from hot ethanol to afford the desired product as white needles (3.75 g, 13.9 mmol, 35%): mp 97−98 °C; IR (Nujol) 2920, 2854, 1714, 1648 cm^{-1}; ^1H NMR ($CHCl_3$, ppm) 3.60 (s, 3H), 3.62 (s, 3H), 6.92 (d, 1H, J = 8.4 Hz), 7.01 (td, 1H, J = 0.9, 7.5 Hz), 7.39 (dd, 1H, J = 1.2, 7.3 Hz), 7.59 (m, 3H), 7.72 (dd, 1H, J = 1.9, 7.8 Hz), 7.89 (dd, 1H, J = 1.5, 7.1 Hz); ^{13}C NMR ($CHCl_3$, ppm) 197.5, 167.1, 159.2, 143.7, 134.4, 131.8, 131.4, 129.5, 127.9, 127.8, 127.6, 120.4, 112.1, 110.2, 56.0, 52.1; GC/CIMS (CH_4/NH_3(g)) *m/z* 270.95 (MH^+). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H 5.22. Found: C, 71.10; H, 5.25.

Methyl 2-(2,5-Dimethoxybenzoyl)benzoate (7b). Monomethyl phthalate (2.6 g, 14.4 mmol) was dissolved in trifluoroacetic anhydride (8 mL), and the solution was heated to 55 °C for 15 min. Hydroquinone dimethyl ether (2.0 g, 14.4 mmol) was added in one portion and the resulting solution maintained at 55 °C for 6 h. After cooling the solution was poured into 100 mL of saturated sodium bicarbonate and extracted with 2 × 50 mL of ether. The combined organic extracts were washed with 1 × 100 mL of saturated sodium bicarbonate and 1 × 100 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. This oil was purified via flash chromatography (SiO_2, 10−35% EtOAc in hexane) to afford the desired product as a white solid (3.36 g, 11.2 mmol, 78%): mp 85−86 °C; IR (Nujol) 2924, 2854, 1713, 1652 cm^{-1}; ^1H NMR ($CHCl_3$, ppm) 3.48 (s, 3H), 3.65 (s, 3H), 3.81 (s, 3H), 6.86 (d, 1H, J = 9.0 Hz), 7.05 (dd, 1H, J = 3.2, 9.0 Hz), 7.36 (m, 2H), 7.52 (m, 2H), 7.92 (d, 1H, J = 7.7 Hz); GC/CIMS (CH_4/NH_3(g)) *m/z* 300.95 (MH^+). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.92; H, 5.42.

General Procedure for the Photochemical Reduction of Keto Esters 1a−f. Solutions of ketone in the desired solvent system and any other desired reagent were prepared and placed in a jacketed Pyrex flask, equipped with stirbar and rubber septum. The solutions were cooled by a circulating water bath and degassed by bubbling dry argon through them for 20 min. The solutions were then irradiated for the indicated time, with continuous stirring and while under a positive pressure of argon, with a medium pressure 450 W Hg lamp at a distance of 5 cm. In the cases of photoreduction using amines, the reaction mixtures were partitioned between 1 M HCl and EtOAc. The aqueous layer was extracted twice more with EtOAc, and the combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated *in vacuo*. In cases using 2-propanol the solvent was removed *in vacuo*. The product mixtures were analyzed by GC, TLC, and NMR. The crude material was dissolved in $CDCl_3$ and an internal standard added (mesitylene). Product yields were determined by integrating the appropriate product signals relative to the NMR signal from a known amount of the added standard. Where possible both the aromatic and aliphatic NMR signals from the standard were used and the results averaged. As many signals as possible from the products were also used. The relaxation delay was set to 3 s.

Dodecyl 2-benzoylbenzoate (1.21 g, 3.07 mmol) was irradiated for 6 h as a 0.1 M solution in 1:1 benzene:acetonitrile with cyclohexylamine (3.5 mL, 30.7 mmol). The crude mixture was worked up as indicated above, and mesitylene (0.14 mL, 1.0 mmol) was added. GC and NMR indicated only two products which were identified as 3-phenylphthalide and 1-dodecanol by coinjection with authentic samples. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 95%; 1-dodecanol, 95%. The crude mixture was purified via flash chromatography (silica, 9:1 hexane:EtOAc eluent) to afford 1-dodecanol (510 mg, 2.74 mmol, 90%) and 3-phenylphthalide (475 mg, 2.27 mmol, 74%).

Dodecyl 2-benzoylbenzoate (0.245 g, 0.62 mmol) was irradiated as a 0.01 M solution in 1:1 benzene:2-propanol. After 5 h the solvent was removed *in vacuo* and redissolved in $CDCl_3$, and mesitylene (0.025 mL, 0.179 mmol) was added. TLC and NMR indicated only two products which were identified as 1-dodecanol and the dimer of 3-phenylphthalide. From the NMR the yields obtained are as follows: 3-phenylphthalide dimer, 95%; 1-dodecanol, 95%.

Cyclododecanyl 2-benzoylbenzoate (0.150 g, 0.38 mmol) was irradiated for 18 h as a 0.1 M solution in 1:1 benzene:acetonitrile with cyclohexylamine (0.43 mL, 3.8 mmol). The reaction mixture was worked up as indicated above, and mesitylene (0.015 mL, 0.108 mmol) was added. GC and NMR indicated only two products which were identified as 3-phenylphthalide and cyclododecanol by coinjection with authentic samples. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 80%; cyclododecanol, 85%.

Cyclododecanyl 2-benzoylbenzoate (0.100 g, 0.26 mmol) was irradiated as a 0.01 M solution in 1:1 benzene:2-propanol. After 18 h the solvent was removed *in vacuo* and the residue redissolved in $CDCl_3$. Mesitylene (0.025 mL, 0.18 mmol) was added. TLC and NMR showed that the main products were cyclododecanol and the dimer of 3-phenylphthalide. There was a trace of 3-phenylphthalide present as well. From the NMR data the yields obtained are as follows: 3-phenylphthalide dimer, 85%; cyclododecanol, 85%.

Cholesteryl 2-benzoylbenzoate (0.597 g, 1.0 mmol) was irradiated as a 0.1 M solution in 1:1 benzene:acetonitrile with cyclohexylamine (1.14 mL, 10 mmol). The reaction mixture was worked up as indicated above, and mesitylene (0.045 mL, 0.324 mmol) was added. NMR indicated only two products which were identified as 3-phenylphthalide and cholesterol by TLC. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 95%; cholesterol, 100%.

Cholesteryl 2-benzoylbenzoate (0.241 g, 0.41 mmol) was irradiated as a 0.01 M solution in 1:1 benzene:2-propanol. After 18 h the solvent was removed *in vacuo* and the residue redissolved in $CDCl_3$. Mesitylene (0.02 mL, 0.144 mmol) was added. TLC and NMR showed a mixture of products. Two were identified as cholesterol and the dimer of 3-phenylphthalide. From the NMR data the yields obtained are as follows: cholesterol, 20%; 3-phenylphthalide dimer, 5%.

Geranyl 2-benzoylbenzoate (0.610 g, 1.68 mmol) was irradiated for 5 h as a 0.1 M solution in 1:1 benzene:acetonitrile with cyclohexylamine (1.92 mL, 16.8 mmol). The reaction mixture was worked up as indicated above, and mesitylene

(0.078 mL, 0.56 mmol) was added. GC and NMR indicated the presence of only 3-phenylphthalide and geraniol. From the NMR data the yields obtained are as follows: geraniol, 85%; 3-phenylphthalide, 80%.

Geranyl 2-benzoylbenzoate (0.905 g, 2.5 mmol) was irradiated as a 0.1 M solution in 1:1 benzene:acetonitrile with *sec*-butylamine (2.5 mL, 25 mmol). After 5 h the solvent was removed *in vacuo* and the residue redissolved in $CDCl_3$. Mesitylene (0.071 mL, 0.51 mmol) was added to the solution. GC and NMR indicated the presence of only 3-phenylphthalide and geraniol. From the NMR data the yields obtained are as follows: geraniol, 90%; 3-phenylphthalide, 70%.

5′-((2-Benzoyl)benzoyl)-2′,3′-isopropylideneuridine (0.246 g, 0.50 mmol) was irradiated for 5 h as a 0.1 M solution in 1:1 benzene:acetonitrile with *sec*-butylamine (0.5 mL, 5 mmol). The reaction mixture was worked up as indicated above, and mesitylene (0.047 mL, 0.33 mmol) was added. NMR and TLC showed 3-phenylphthalide and 2′,3′-isopropylideneuridine to be the major products along with a number of unidentified minor products. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 75%; 2′,3′-isopropylideneuridine, 60%.

5′-((2-Benzoyl)benzoyl)-2′,3′-isopropylideneuridine (0.246 g, 0.50 mmol) was irradiated for 18 h as a 0.1 M solution in 1:1 benzene:acetonitrile with *sec*-butylamine (0.5 mL, 5 mmol). A uranium glass filter was employed to eliminate radiation with $\lambda < 350$ nm. The reaction mixture was worked up as indicated above, and mesitylene (0.047 mL, 0.33 mmol) was added. NMR and TLC showed 3-phenylphthalide and 2′,3′-isopropylideneuridine to be the only products. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 80%; 2′,3′-isopropylideneuridine, 90%.

Dodecyl 2-benzoylbenzenethioate (0.434 g, 1.06 mmol) was irradiated as a 0.1 M solution in 1:1 benzene:acetonitrile with cyclohexylamine (1.25 mL, 11 mmol). After 5.5 h a precipitate had formed. The solvent was removed *in vacuo*, and the residue was dissolved in hexane, chilled, and filtered. The precipitate was identified as 3-phenylphthalidyl dimer (0.100 g, 0.24 mmol, 45%) by NMR. The filtrate was then worked up as usual, and mesitylene (0.04 mL, 0.288 mmol) was added. Four products were identified by GC and coinjection with authentic samples. They were 3-phenylphthalide, 3-phenylphthalidyl dimer, 1-dodecanethiol, and dodecane disulfide. From the NMR data the yields obtained are as follows: 3-phenylphthalide, 20%; 1-dodecanethiol, 60%; dodecane disulfide, 20%. It was impossible to determine the amount of 3-phenylphthalidyl dimer remaining in solution.

Preparation and Photolysis of samples for Isotope, Substituent, and Solvent Effect Studies. Samples were prepared by adding substrate, solvent, and amine to a Pyrex test tube with screw-cap top. Argon was bubbled through the resulting solution for 20 min, the test tube sealed, and the sample irradiated at a distance of 5 cm from the lamp while submerged in a water bath. At the end of the photolysis period the solution was poured into 2 M HCl and EtOAc. The layers were separated, and the organic layer was dried over sodium sulfate. Solvent was removed *in vacuo*. The crude reaction mixture was then analyzed by GC, TLC, and NMR to obtain the required data. For the reactions involved in the substituent effect study, the products were not isolated.

JO961638P