Studies on a Dithiane-Protected Benzoin Photolabile Safety Catch Linker for Solid-Phase Synthesis

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Substituted benzoinyl systems **8a**−**g**, differing either in the substitution pattern, type of resin matrix used, or resin loading capacity, were prepared and the kinetics of their photolytic cleavage of Fmoc-β-alanine examined on resin. The linker systems **6a**−**g** were assembled in near-quantitative yield using Corey−Seebach dithiane addition. The dithiane group that serves as a safety catch against premature photoreaction was removed by either oxidation or alkylation. Analytical methods that include FTIR and ^{13}C gel-phase NMR spectroscopy were used for rapid reaction monitoring and sample characterization on resin. A survey of different substituted systems **8c**−**f** for releasing Fmoc-β-alanine confirmed that the 3-alkoxybenzoin linker photocleaves most rapidly to give the highest yield ($\tau_{1/2}$ = 6.7 min; 98% yield). Lowering the resin loading from 0.59 mmol/g in **8a** to 0.26 mmol/g in **8b** improved the cleavage kinetics to $\tau_{1/2}$ = 2.6 min, 92% yield. Tentagel resin **8g** exhibits similar photocleavage kinetics in both organic and aqueous media and when compared to the polystyrene counterpart, **8a**. The 3-alkoxybenzoin linker **6a** was also loaded with aryl carboxylic acids (**12h,i**) and hindered Fmoc-protected amino acids (**12j**−**l**) with varying degrees of success (57−100%) and dithiane deprotected (70−80%, **13h**−**l**) followed by photocleavage with comparable efficiencies (89−93% after 60 min).

Introduction

The rapidly growing field of combinatorial chemistry to generate libraries of molecules has renewed interest in the use of solid-phase organic synthesis as a convenient means of assembling molecules.[1,2] In the construction of a library of small molecules on solid support, the linker that connects the compounds to the resin has an important role. It must be stable to the diverse reactions employed on solid phase and yet be cleaved under conditions that will not affect the released compounds. While many chemically cleavable linkers have emerged in recent years, they are by no means universal and often require some post-cleavage purification to remove the cleavage reagent. One alternative is the photolytic cleavage strategy,[3] which offers a mild, neutral, and orthogonal method of cleavage. Such a strategy is attractive for compound screening, as the release of the molecules can occur after extensive washing of the resin, thereby liberating pure compound suitable for biological assay without suffering contamination by cleavage reagents.

A number of photolabile supports have been employed in the synthesis of peptides, in particular, *o*-nitrobenzyl derivatives[4] and derivatives of phenacyl[5] groups. The recently reported *o*-nitrobenzyl linkers based on the α-methyl-6-nitroveratryl chromophore[6,7] give rapid cleavage kinetics (95% yield in 3 h) in both organic and buffered aqueous solvents. However, the α-methyl-6-nitroveratryl based linker requires lengthy synthesis, is sensitive to sunlight, has widely varying quantum yields depending on the identity of the leaving group, and also generates a reactive nitroso chromophore on the resin support. The phenacyl linkers, on the other hand, suffer from slow cleavage kinetics, are sensitive toward mildly nucleophilic reagents, and cyclize easily to form diketopiperazines when used in peptide synthesis.[8−10]

Researchers have addressed these shortcomings, and several alternative photocleavable linkers have been reported. One such linker based on 3′-methoxybenzoin was used in solution by Chan and Rock[11] and recently employed on solid phase in our group.[12] Sheehan and Wilson first investigated the benzoin chromophore **1** as a possible photolabile protecting group for carboxylic acids in 1964.[13] Among the minor photoproducts was the photocyclized 2-phenylbenzofuran **3** and its photodimers. The efficiency of the photocyclization was shown to be highly dependent on the nature of substituents on the phenyl ring, with the *m*-methoxy substitution giving the highest yield of benzofuran. This observation led to the 3,5-dimethoxybenzoin system **2**,[14] whose carboxylic esters release the free acids quantitatively at 365 nm with a high quantum yield (0.64) to form the inert 2-phenyl-5,7-dimethoxybenzofuran **4**, as the only byproduct. Few other reports relevant to the photochemistry of benzoin derivatives appeared until the early 1990's, when Givens,[15−17] Baldwin,[18] Pirrung,[19] and Corrie[20] independently dem-

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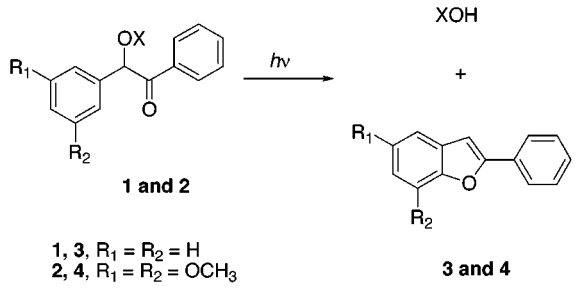

onstrated their usefulness for masking phosphate esters and inorganic phosphates. Derivatization of benzoin to its carbonate has allowed the protection of a 5′-hydroxyl group in nucleosides[21,22] as well as a variety of other alcohol,[21] amine,[23] and thiol[21] derivatives. Benzoin esters,[24] carbonates,[21] and carbamates[25] of meta-substituted benzoins have been shown to exhibit similar photolytic properties. Benzoinyl photolabile groups have also been used to generate caged molecules (for, e.g., neurotransmitters such as amino acids,[26] cAMP,[15] and biologically active peptides[27]), to prepare large arrays of biopolymer sequences[22] and in the design of a photolabile linker.[11] In conclusion, the literature suggests that, in comparison with *o*-nitrobenzyl photochemistry, the 3′,5′-dimethoxybenzoin system exhibits increased stability of photobyproducts, improved photoefficiency, and compatibility in the photorelease of a more diverse range of functionalities. Following the initial success with the 3-alkoxy benzoin based linker,[12] we have further studied (i) linker assembly on solid support, (ii) nontoxic methods of orthogonal dithiane deprotection, (iii) photolytic efficiency and kinetics on solid support by substituent effect, (iv) the effect of loading site density and types of resin matrix on photolysis, and (v) the loading and release of a range of substrates. These studies should now enable more general and optimal utilization of the system.

Results and Discussion

Synthesis. Various aromatic substituted derivatives of the linker systems were prepared on resin using the Corey−Seebach dithiane addition.[28,29] To prepare dithiane derivative **6a**, 3-hydroxybenzaldehyde was immobilized on chloromethylpolystyrene (1.05 mmol/g, Aldrich) by alkylation, providing a stable ether linkage.[12] The aldehyde **5a** was then reacted with lithiated 2-phenyl-1,3-dithiane as previously described,[12] affording **6a** (Scheme 1). The reaction sequence was monitored using FT-IR spectroscopic analysis of the relative intensity of the aryl aldehyde peak at 1697 cm^{-1} to a polystyrene backbone peak at 1600 cm^{-1} and then disappearance of the same aryl aldehyde peak after dithiane coupling. The loading of the resin at this point was determined to be 0.80 mmol/g by elemental analysis of sulfur, implying near-quantitative yield over the two steps. Qualitative characterization of the modified resin by gel-phase ^{13}C NMR spectroscopy was possible due to the distinct methylene signals of the dithiane at 24.7, 27.0, and 27.2 ppm (Figure 1, spectrum b). We also found that preforming the hydroxybenzaldehyde or dithiane anions in solution using slightly less than stoichiometric amounts of base, prior to mixing with the resin suspension, produced less intensely-colored resins in either reactions, which is important for UV penetration during photolysis. Fmoc-protected *β*-alanine was attached to resin **6a** using diisopropylcarbodiimide coupling to afford the ester **7a**. The extent of ester formation was measured by Fmoc-release to be 0.62 mmol/g (95%). A gel-phase ^{13}C NMR spectrum of the ester **7a**, acquired over just 1 h of NMR time, showed all the substrate peaks very clearly and in good agreement with that of an authentic solution sample of Fmoc-*β*-alanine (Figure 1, spectra a and c).

To facilitate photocleavage, the dithiane protecting group can potentially be removed under a range of conditions. Three general strategies have been used in solution to enhance the nucleofugacity of sulfur; metal coordination, alkylation, and oxidation.[31] Even though heavy metal coordination such as in the case of mercury(II) reagents is the most popular method for deprotection of *S*,*S*-acetals in solution, its high toxicity is undesirable on solid phase since any trapped Hg(II) residual will affect subsequent biological assays of the cleaved material. To further improve the methods available for deprotection of the linker, S-alkylating agents were explored. Treatment of resin **7a** with methyl triflate for 20 min followed by a basic resin wash produced complete deprotection according to the disappearance of the dithiane methylene signals in the ^{13}C gel phase NMR spectrum (Figure 1, spectrum d). However, sulfur analysis on resin **8a** consistently indicated the presence of about 20% of the dithiane moiety, suggesting that gel-phase ^{13}C NMR spectroscopy is probably only sensitive to a minimum loading of about 20% of our resin capacity, which translates to roughly 0.1 mmol/g. Deprotection using periodic acid also worked to the same extent for our systems, as indicated by nitrogen analysis of **8a** (83%) as well as gel-phase ^{13}C NMR spectroscopy. Retreating either resin **8a** or the photocleaved resin with periodic acid or methyl triflate afforded a further 5−10% of dithiane deprotection by sulfur analysis, also supported by further substrate release on subsequent photolysis. A new ketone peak at 1697 cm^{-1} was observed in the gel-phase FTIR spectrum.

To investigate the effect of substituents on the kinetics of resin photolysis, esters **8c**−**f** were prepared. 3′,5′-

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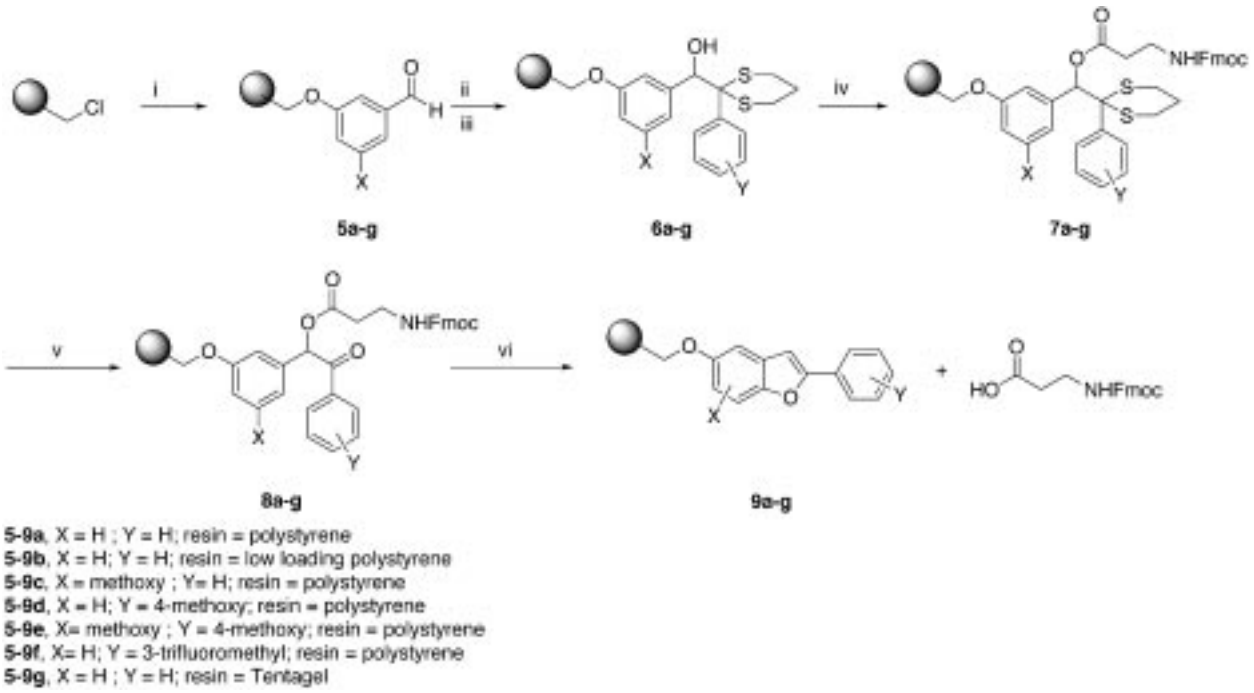
Scheme 1



Dimethoxybenzoin[14,24] and 3′,4,5′-trimethoxybenzoin[25] systems, which are solution equivalents of systems **8c** and **8e**, respectively, exhibit improved photocleavage kinetics in solution over the 3-methoxybenzoin system. Benzoin systems such as **8d** and **8f**, however, have not previously been studied in solution. For the synthesis of **5c** and **5e**, 3-hydroxy-5-methoxybenzaldehyde was prepared by monomethylating the dihydroxy substrate[32] while the synthesis of **6d**, **6e**, and **6f** required the preparation of 2-(4′-methoxyphenyl)-1,3-dithiane and 2-(3′-trifluoromethylphenyl)-1,3-dithiane from the corresponding aldehydes following the Corey−Seebach procedure.[28] As additional variations, a lower capacity polystyrene resin and Tentagel resin (0.32 mmol/g) were also used to construct systems **8b** and **8g** with the same substitution pattern as the parent **8a**. The lower loading resin **5b** was prepared by addition of a 3:7 mixture of hydroxybenzaldehyde and phenoxide anions to the same Merrifield resin used for making **5a**. The effect of loading and resin matrix on photoefficiency was investigated using systems **8b** and **8g**, respectively. Preparation of esters **8b**−**f** was carried out using the protocol as described for the preparation of **8a**, in similar high yields despite the difference in substitution pattern, resin matrix or loading capacity.

Photolysis Studies. An aliquot of the resin with deprotected linker **8a** formed by either methyl triflate or periodic acid treatment of **7a** was irradiated at 350 nm in THF/methanol (3:1). The resin suspension was agitated by bubbling with a stream of nitrogen throughout the photolysis to ensure even exposure of the resin beads to UV irradiation. Photolytic experiments carried out without nitrogen bubbling resulted in significantly poorer cleavage kinetics, confirming that polystyrene resin beads are not totally transparent to UV radiation. The use of Fmoc-serine as an internal solution standard allowed for accurate quantification of the Fmoc-β-alanine release by HPLC at various time intervals. After 120 min, the photocleaved resin **9a** was analyzed by Fmoc-analysis and gave a residual loading that agreed to within 5% of that obtained from HPLC analysis of the photolyzate. ^{1}H NMR spectroscopy of the crude photolyzate showed traces of polymerized THF as the only impurity, which could be eliminated by reducing the photolysis time from 2 h to 30 min. The ^{13}C gel-phase NMR spectrum of the residual resin indicated almost complete loss of the Fmoc-protected β-alanine (Figure 1, spectrum e).

On first attempt, photolysis of **8a** (0.54 mmol/g according to sulfur analysis) to release Fmoc-β-alanine appeared to follow first-order kinetics, reaching a maximum yield of 98% after 120 min of photolysis time (Figure 2, trace a). Subjecting the resultant resin to a repeated photolysis after extensive washing and drying did not yield further product in solution. We considered that the photoreactive benzoin as well as the nonreactive resin-bound benzofuran **9a**, which has an absorbance at 300 nm and fluorescence emission maximum at 396 nm when excited at 310 nm, could serve as internal light filters to slow the photolysis or even to render the core reaction sites inaccessible to UV photons. To test this hypothesis, resin **8b** with a lower linkage site density of 0.26 mmol/g (according to Fmoc analysis) was photocleaved. This system also released a maximum yield of 92%, but its half-life was roughly halved compared to **8a** (Figure 2, trace b). All other substitution patterns in system **8c**−**f** did not show enhanced cleavage kinetics compared to the parent system **8a** (Figure 2, traces c−f, Table 1). Again, it is probable that the high extinction coefficient of the substituted benzoins and also the substituted benzofuran photoproduct at $\lambda > 350$ nm may have affected the cleavage rate and efficiency by serving as internal light filters. Indeed, the intensity of the visible coloration of the resins increases with the level of substitution of the benzoinyl rings as observable in systems **8a** < **8c** < **8e**. This hypothesis is supported in part by the observation that resin **8b** has a lower photocleavage half-life (2.6 min)

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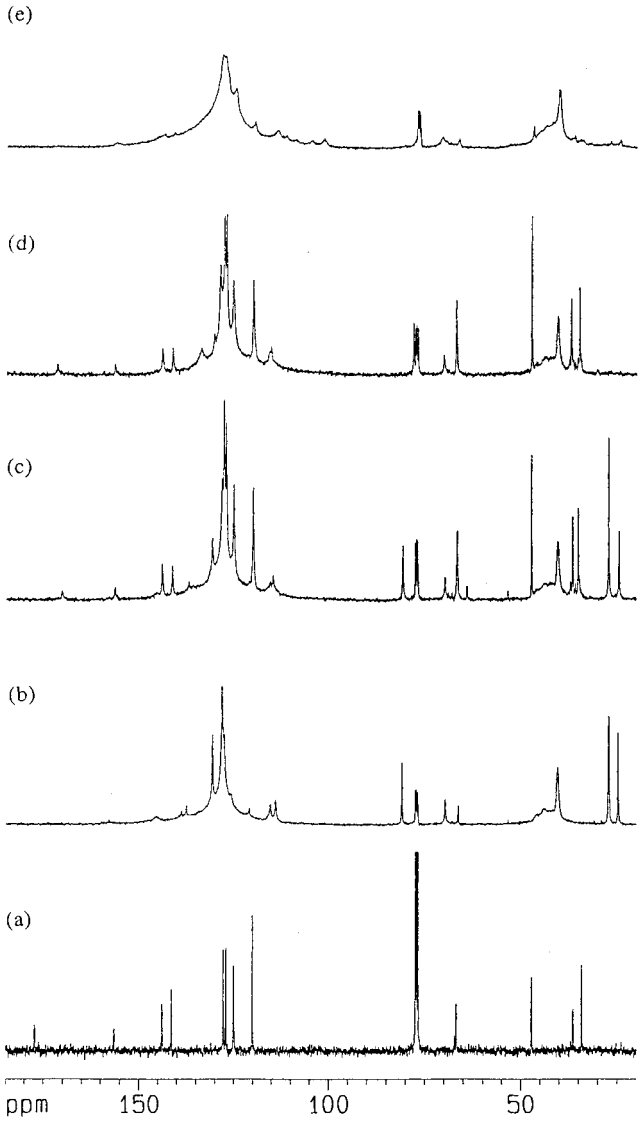


Figure 1.

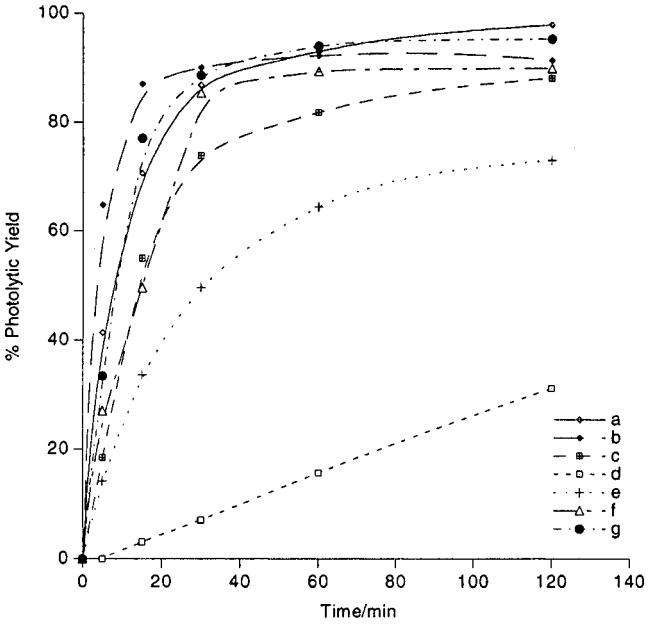


Figure 2.

Table 1. Measured Photolysis Half-Lives and % Yield after 120 Min for Resins 8a−g

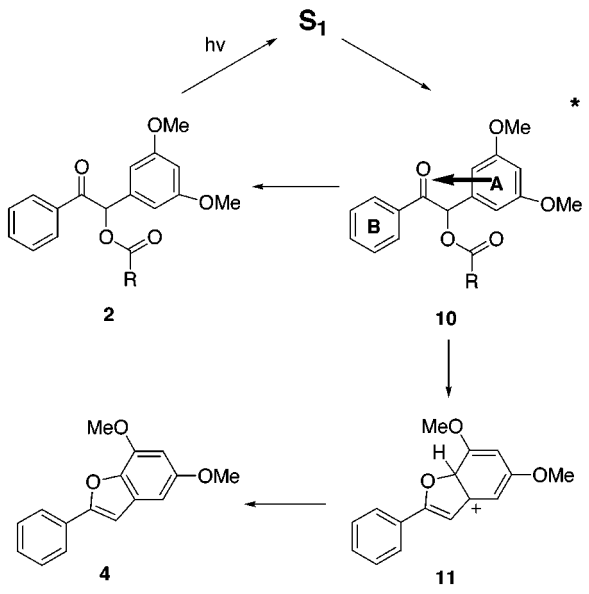
entry	half-life ($\tau_{1/2}$)[a]/min	% yield after 120 min[b]
8a	6.7	98
8b	2.6	92
8c	12.4	88
8d	NA[c]	31
8e	18.1	73
8f	13.0	90
8g	7.8	95

[a] Time taken for half Fmoc-β-alanine to be released assuming total release at 120 min. [b] Measured by HPLC UV analysis of the photolysate, based on the quantity of *deprotected* linker present prior to photolysis. [c] Photocleavage profile did not appear to follow first-order kinetics.

than **8a** (6.7 min) probably due to a reduced optical density.

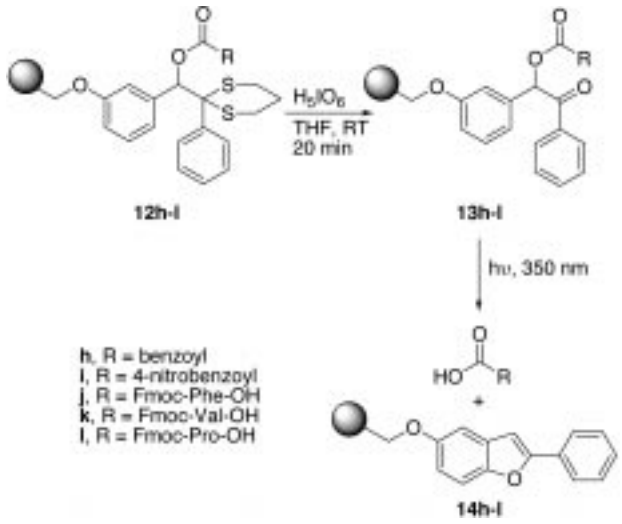
The difference in photocleavage kinetics observed within systems **8c**−**f** is more difficult to rationalize. To comprehend the effect of substituents on photoefficiency, an appreciation of the photocyclization mechanism is necessary. A number of mechanistic hypotheses have been proposed by several groups.[14,16,19,25] Recently, Corrie and co-workers[24] presented spectroscopic evidence that in 3′5′-dimethoxybenzoin esters **2** (Scheme 2) the primary photochemical event is heterolytic bond cleavage of the ester bond, assisted by electronic interaction between the electron rich dimethoxybenzene ring (A) and the singlet n,π* excited carbonyl group of the acetophenone moiety (B), to form an intramolecular exciplex **10** that can either return to **2** or react to give cyclohexadienyl cation **11**, the precursor of the benzofuran product **4**. The photoefficiency of systems **8c**−**f** appeared to decrease from **8c** = **8f** > **8e** > **8d** (see Figure 2, traces c−f, and Table 1). Incidentally, the electronic asymmetry between the aromatic rings (i.e., A−B) also was greatest in resins **8c** and **8f** followed by **8e** then **8d**. Therefore, it is probable that the photocleavage kinetics of substituted benzoins is directly related to the electronic difference between the

Scheme 2



two aromatic rings within the benzoinyl systems. The more electron-rich the unconjugated aromatic ring (A) compared to the phenacyl aromatic ring (B), the greater the charge-transfer interaction between the rings and the greater the photoefficiency.

Scheme 3



Studies on Tentagel resin **8g** demonstrated a very similar photocleavage profile compared to resin **8a** (Figure 2, trace g, and Table 1). This shows that resin matrix does not influence the photochemical reaction profile in our systems even though polystyrene- and Tentagel-based resins have been shown to have rather different chemical reaction profiles.[33] A photolysis experiment of resin **8g**, carried out in 3:1 MeCN/H_2O gave a similar cleavage kinetics profile as that in 3:1 THF/MeOH to liberate clean isolable Fmoc-β-alanine (data not shown for clarity). This is in good agreement with Corrie and co-workers' finding where they observed that the quantum yield for 3′,5′-dimethoxybenzoin acetate did not change by more than 10−15% in a range of solvents that included THF, Et_2O, CH_3CN, and 1:1 H_2O/CH_3CN.[24]

Photolytic Release of Other Carboxylic Acid Substrates. To test the generality of the linker, a variety of other carboxylic substrates were loaded, dithiane deprotected, and photocleaved (Scheme 3). Benzoyl chloride and 4-nitrobenzoyl chloride were reacted with resin **6a** using standard conditions to afford benzoyl esters **12h** and **12i**, respectively, in near-quantitative yield according to sulfur analysis. The hindered Fmoc-protected amino acids Fmoc-Phe-OH, Fmoc-Val-OH, and Fmoc-Pro-OH were also loaded using the same protocol as for loading Fmoc-β-Ala-OH but to varying degree of efficiencies according to Fmoc analysis on the resin-bound amino acids **12j**−**l** (100%, 65%, and 57% for Phe, Val, and Pro, respectively), revealing the influence of the bulky dithiane group on loading efficiency. Using other coupling reagents such as HATU and PyBOP for loading the hindered substrates or converting the amino acids to acid chlorides using oxalyl chloride/pyridine prior to reacting with resin **6a** resulted in much poorer (<30%) loading efficiencies. Subsequent deprotection of resin **12h**−**l** using periodic acid followed by photolysis of the resultant ketones **13h**−**l** was carried out with efficiencies independent of the carboxylic acid substrates (Table 2).

Conclusion

We have demonstrated the efficient synthesis and characterization of a dithiane-protected linker on resin. A clean and efficient way of dithiane deprotection on solid phase using methyl triflate has been developed (85−90% yield). A study of a number of substituted benzoin systems **8a**−**f** demonstrated the effect of benzoinyl substitution on photoefficiency with the 3-alkoxy substitution in a low-capacity resin, **8b** giving the best photocleavage kinetics of $\tau_{1/2} = 2.6$ min and 92% yield after 120 min. Studies carried out using other carboxylic acid substrates showed that loading efficiency is sensitive to steric bulk with yields of 50−60% for the bulkiest substrates improving to quantitative loading for less hindered acids such as Fmoc-Phe-OH and Fmoc-β-Ala-OH. Dithiane deprotection and photocleavage efficiencies were largely independent of the substrates. These studies appear to support its general utility for releasing carboxylic acids. More efficient dithiane removal on solid phase or the use of an alternative protecting group may lead to further improvements. Furthermore, the efficient release of compounds from Tentagel (**8g**) into biologically compatible solvents using the linker opens the way for its application in biological screening.

Table 2. Loading, Dithiane Removal, and Photocleavage Percent Yields of Resins 12h−l in Comparison with 7a

entry	loading[a]/%	dithiane removal[b]/%	photolysis/% after 60 min[c]	substrate released
7a	100	83	93	β-Ala
12h	99	74	92	benzoic
12i	98	75	97	4-nitro-Bz
12j	100	74	90	Phe
12k	65	89	87	Val
12l	57[d]	89	75	Pro

[a] Percent yield calculated from Fmoc analysis. [b] Percent yield calculated from sulfur analysis. [c] Percent yield measured by HPLC UV analysis, based on the quantity of *deprotected* linker present prior to photolysis. [d] Photocleavage profile over 120 min showed maximum yield of 4-nitrobenzoic acid (98%) at 30 min followed by degradation of the acid (see the Supporting Information for photorelease kinetics profile).

Experimental Section

General Methods. Chemicals and Merrified resin (1.05 mmol of Cl/g) were purchased from Aldrich Chemical Co. and used without further purification. Bromomethyl Tentagel resin (0.32 mmol of Br/g) and Fmoc-protected amino acids were purchased from Novabiochem and used without further purification. The loading of the commercial resins was determined by halogen elemental analysis, prior to use. Solvents for the photolysis experiments were freshly distilled. All other anhydrous solvents were purchased from Aldrich or Fluka Chemical Corp. General washing procedure for resin samples: for every 100 mg of resin, three aliqouts of 2 mL of DMF, THF, THF/H_2O, THF, MeOH, THF, and dichloromethane (DCM) were used in succession. FTIR spectra of resin samples were taken as a gel in CH_2Cl_2. ^{13}C gel-phase NMR data were acquired on DRX400 Bruker in $CDCl_3$, and chemical shifts are quoted relative to solvent signals. Standard conditions were used: acquisition time = 0.1 s, 10 ns delay between pulses, no. of scans = 3.5×10^5). Elemental analyses were performed by Zeneca Pharmaceuticals, U.K. Fmoc analysis was performed on a known amount of resin sample (5−6 mg) in 10 or 20 or 30 mL of 20% piperidine in DMF. Photolysis was carried out in a Rayonet photochemical reactor fitted with 8 × 8 W RMR 350 nm lamps. Calcd % S in resins **6a,c**−**g** was based on 100% conversion of the starting Merrifield or bromomethyl Tentagel resin to the dithiane.

Resin-Bound Benzaldehydes 5a,d,f. Sodium hydride (0.24 g, 6 mmol, 300 mol %) was added in one aliquot to a stirred solution of 3-hydroxybenzaldehyde (0.70 g, 5.7 mmol, 285 mol %) in anhydrous DMF (10 mL) under argon at 0 °C, and stirring was continued for 1 h at room temperature. This

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solution was syringed to a suspension of Merrifield resin (2 g, 2 mmol, 100 mol %) in anhydrous DMF (10 mL) and the mixture shaken under argon for 12 h at 25 °C. The resin was filtered, washed, and dried under vacuum to give the resin-bound aldehydes **5a**,**d**,**f**: IR 1697 cm^{-1}.

Resin-Bound Benzaldehyde 5b. Same procedure as for **5a** except a mixture of phenol (3 × 70 mol %) and 3-hydroxybenzaldehyde (3 × 30 mol %) was used: IR 1697 cm^{-1}.

Resin-Bound Benzaldehyde 5c,e. Same procedure as for **5a** except 3-hydroxy-5-methoxybenzaldehyde[32] (300 mol %) was used: IR 1700 cm^{-1}.

Resin-Bound Benzaldehyde 5g. Same procedure as for **5a** except bromomethyl Tentagel resin (100 mol %) was used: IR = 1697 cm^{-1}.

Resin-Bound Dithiane-Protected Benzoin 6a. To a stirred solution of 2-phenyl-1,3-dithiane (0.78 g, 4 mmol, 400 mol %) in anhydrous THF (4 mL) under argon at −78 °C was added *n*-butyllithium (1.76 mL, 3.5 mmol, 350 mol %), and stirring was continued for 10 min at 0 °C. This solution was transferred via a cannula to a suspension of aldehyde resin **5a** (1.0 g, ∼1 mmol, 100 mol %) cooled to 0 °C in THF (6 mL), and the mixture was gently stirred at 0 °C. The aldehyde IR peak was completely lost after stirring for 1 h. The resin suspension was quenched with dilute 1 N HCl (5 mL), and the resin was filtered, washed, and dried under vacuum to give the resin-bound dithiane-protected benzoin **6a**: loading = 0.80 mmol/g (99%); IR 3583, 3445 (b) cm^{-1}; δ_C 138.8, 137.5, 130.7, 128.1, 127.5, 126.0, 115.3, 113,9, 80.9, 69.7, 66.3, 27.2, 27.0, 24.7. Anal. Calcd: S, 5.18 Found: S, 5.1.

Resin-Bound Dithiane-Protected Benzoins 6b,c,g. Same procedure as for **6a** except aldehyde resins **5b**, **5c**, and **5g** (100 mol %) were used, respectively.

Resin 6b: loading = 0.27 mmol/g. Found: S, 1.7.

Resin 6c: loading = 0.81 mmol/g (103%); IR 3583, 3445 (b) cm^{-1}. Calcd: S, 5.1. Found: S, 5.3.

Resin 6g: loading = 0.29 mmol/g (100%); IR 3514 (b) cm^{-1}. Calcd: S, 1.9. Found: S, 1.9.

Resin-Bound Dithiane-Protected Benzoin 6d,e. Same procedure as for **6a** except 2-(4-dimethoxyphenyl)-1,3-dithiane[28] (0.30 g, 1.5 mmol, 300 mol %) and aldehyde resin **5d** or **5e** (100 mol %) were used.

Resin 6d: loading = 0.81 mmol/g (103%); IR 3583, 3445 (b) cm^{-1}. Calcd: S, 5.1. Found: S, 5.2.

Resin 6e: loading = 0.78 mmol/g (101%); IR 3584, 3445 (b) cm^{-1}. Calcd: S, 4.9. Found: S, 5.0.

Resin-Bound Dithiane-Protected Benzoin 6f. Same procedure as for **6a** except 2-(3-trifluoromethylphenyl)-1,3-dithiane and aldehyde resin **5f** (100 mol %) were used: loading = 0.78 mmol/g (101%); IR 3582, 3445 (b) cm^{-1}. Calcd: S, 4.9. Found: S, 5.0.

General Fmoc-Protected *β*-Alanine Loading Procedure (7a−g). Diisopropylcarbodiimide (94 *μ*L, 0.6 mmol, 300 mol %) followed by diisopropylethylamine (104 *μ*L, 0.6 mmol, 300 mol %) was syringed into a solution of dithiane-protected benzoin resin **6a**−**g** (200 mg, ∼0.2 mmol, 100 mol %), Fmoc-protected *β*-alanine (168 mg, 0.6 mmol. 300 mol %), (dimethylamino)pyridine (10 mg), and HOBt (10 mg) in anhydrous DMF (2 mL) under argon at room temperature, and the mixture was gently stirred for 5 h. The resin was filtered, washed, and dried under vacuum to give the resin-bound Fmoc-protected amino acid **7a**−**g**. Loading was determined by Fmoc analysis of **7a**−**g**.

Resin 7a: loading = 0.62 mmol/g (95%); IR 1725 (b), 3445, 3368 cm^{-1}; δ_C 170.2, 156.3, 143.9, 141.2, 136.9, 130.7, 128.2, 127.6, 127.0, 125.0, 119.9, 115.3, 114.5, 80.6, 69.7, 66.6, 47.2, 36.5, 35.0, 27.2, 24.6. Found: N, 1.1. S, 4.1.

Resin 7b: loading = 0.24 mmol/g (100%); IR 1725 (b) cm^{-1}. Found: N, 0.4; S, 1.5.

Resin 7c: loading = 0.62 mmol/g (97%); IR 1728 (b), 3445, 3368 cm^{-1}. Found: N, 0.9; S, 4.6.

Resin 7d: loading = 0.59 mmol/g (92%); IR 1726 (b), 3445, 3368 cm^{-1}. Found: N, 0.9; S, 4.1.

Resin 7e: loading = 0.51 mmol/g (81%); IR 1724 (b), 3445, 3368 cm^{-1}. Found: N, 0.8; S, 4.2.

Resin 7f: loading = 0.61 mmol/g (97%); IR 1725 (b), 3445, 3368 cm^{-1}. Found: N, 0.8; S, 4.2.

Resin 7g: loading = 0.25 mmol/g (94%); IR 1720 (b), 3445, 3368 cm^{-1}. Found: N, 0.4; S, 1.7.

General Procedure for Dithiane Deprotection of 7a−g Using Periodic Acid (8a−g). A solution of periodic acid (68 *μ*L, 0.3 mmol, 300 mol %) in anhydrous THF (1 mL) was added dropwise to a suspension of the Fmoc-*β*-alanine loaded resin **7a**−**g** (100 mg, ∼0.1 mmol, 100 mol %) in anhydrous THF (0.5 mL), and the mixture was gently stirred at room temperature. The dithiane ^{13}C NMR signals were virtually lost after 1 h. The resin was filtered, washed, and dried under vacuum to give the resin-bound dithiane-deprotected benzoin **8a**−**g**.

Resin 8a: Fmoc analysis 0.65 mmol/g; IR 1695 cm^{-1}; δ_C 171.5, 156.5, 144.0, 141.2, 133.7, 130.3, 128.7, 127.6, 127.0, 125.3, 121.1, 115.2, 77.9, 70.3, 66.8, 47.2, 36.5, 34.8. Found: N, 1.0; S, 0.7 (83%, i.e., 0.54 mmol/g of **8a**).

Resin 8b: Fmoc analysis 0.26 mmol/g; IR 1696 cm^{-1}; δ_C 143.9, 141.2, 133.7, 127.6, 127.0, 125.2, 120.8, 119.9, 114.8, 77.9, 69.8, 66.8, 47.2, 36.9, 34.3. Found: N, 0.4; S, 0.2 (87%, i.e., 0.21 mmol/g of **8a**).

Resin 8c: Fmoc analysis 0.61 mmol/g; IR 1696 cm^{-1}; δ_C 171.5, 156.8, 144.0, 141.2, 136.3, 136.2, 128.7, 127.6, 127.0, 125.3, 119.9, 107.6, 101.9, 78.0, 70.0, 66.8, 55.3, 47.2, 36.9, 34.8. Found: N, 0.9; S, 0.9 (78%, i.e., 0.51 mmol/g of **8a**).

Resin 8d: Fmoc analysis 0.50 mmol/g; IR 1682 cm^{-1}; δ_C 171.8, 164.3, 156.1, 143.9, 141.2, 134.9, 127.6, 127.0, 125.3, 120.9, 14.0, 77.6, 70.0, 66.0, 55.4, 47.2, 37.0, 34.9. Found: N, 1.1; S, 0.4 (90%, i.e., 0.56 mmol/g of **8a**).

Resin 8e: Fmoc analysis 0.58 mmol/g; IR 1682 cm^{-1}; δ_C 171.5, 156.5, 143.9, 141.2, 131.2, 127.6, 127.0, 119.9, 113.9, 107.5, 77.7, 70.1, 66.8, 55.4, 47.2, 36.5, 34.8. Found: N, 0.8; S, 0.8 (76%, i.e., 0.40 mmol/g of **8a**).

Resin 8f: Fmoc analysis 0.66 mmol/g; IR 1715 cm^{-1}; δ_C162.0, 156.3, 143.9, 141.2, 127.6, 127.0, 125.1, 119.9, 115.9, 115.1, 77.6, 70.0, 66.8, 47.2, 36.8, 34.6. Found: N, 0.9; S, 0.9 (78%, i.e., 0.50 mmol/g of **8a**).

Resin 8g: Fmoc analysis 0.26 mmol/g; IR 1697 cm^{-1}; δ_C 193.3, 170.9, 158.8, 155.9, 143.5, 140.7, 134.0, 133.7, 133.3, 129.7, 128.3, 127.1, 126.5, 124.7, 120.7, 119.4, 115.0, 114.5, 77.3, 69.0, 66.9, 63.0, 46.6, 36.4, 34.3. Found: N, 0.4; S, 0.5 (69%, i.e., 0.18 mmol/g of **8a**).

Subjecting **8a**,**g** to the same deprotecting conditions yielded a further 5−10% reduction in S content.

General Procedure for Dithiane Deprotection of 7a Using Methyl Triflate. Methyl triflate (136 *μ*L, 0.96 mmol, 1000 mol %) was added dropwise to a suspension of the Fmoc-*β*-alanine loaded resin **8a** (120 mg, ∼0.1 mmol, 100 mol %) in anhydrous DCM (1 mL), and the mixture was gently stirred at room temperature. The dithiane ^{13}C NMR signals were virtually lost after 20 min. The resin was filtered, washed, and dried under vacuum to give the resin-bound dithiane-deprotected benzoin **8a**. Found: N, 1.0; S, 0.9 (79%, i.e., 0.54 mmol/g of **8a**). Subjecting **8a** to the same deprotecting conditions yielded a further 5−10% reduction in S content.

General Photolysis Procedure (9a−g). Dithiane-deprotected resin **8a**−**g** (20 mg) and Fmoc-serine (internal standard, 3 mg) in 3:1 distilled THF/MeOH (12 mL) in a quartz test tube was purged with a stream of nitrogen gas for 10 min. The suspension was UV irradiated for 2 h with constant N_2 bubbling to yield the benzofuranyl resin **9a**−**g** and Fmoc-protected *β*-alanine in solution. Twenty-five microliters of solution was removed at various time intervals and analyzed by HPLC using UV detection at 254 nm. A ^1H NMR spectrum of the cleaved Fmoc-protected *β*-alanine was identical to an authentic sample.

Resin 9a: Fmoc analysis 0.13 mmol/g; δ_C 47.2, 27.2, 24.7.
Resin 9b: Fmoc analysis 0.09 mmol/g.
Resin 9c: Fmoc analysis 0.18 mmol/g.
Resin 9d: Fmoc analysis 0.41 mmol/g.
Resin 9e: Fmoc analysis 0.13 mmol/g.
Resin 9f: Fmoc analysis 0.20 mmol/g.
Resin 9 g: Fmoc analysis 0.07 mmol/g.

General Procedure for Benzoylating Resin 6a (12h,i). To a suspension of resin **6a** (200 mg, ∼0.15 mmol) in

anhydrous pyridine (1 mL) under agron was added benzoyl chloride or 4-nitrobenzoyl chloride (1.5 mmol) diluted in anhydrous DCM (1.5 mL), and the mixture was gently stirred at room temperature for 2 h. The resin was filtered, washed, and dried under vacuum to give the resin-bound dithiane-protected benzoyl ester **12h**) (Found: S, 4.7 (99%, i.e., 0.73 mmol/g)) and the resin-bound dithiane protected 4-nitrobenzoyl ester **12i**. Found: N, 1.0; S, 4.5 (98%, i.e., 0.70 mmol/g).

Other Resin-Bound Dithiane-Protected Fmoc-Protected Amino Acids (12j−l). Compounds **12j−l** were prepared using the same protocol for loading Fmoc-protected *β*-alanine unto resin **6a**. Loading was determined by Fmoc analysis of resins **12j−l**.

For Fmoc-Phe-OH, **resin 12j**: loading = 0.63 (101%). Found: N, 1.0; S, 4.0.

For Fmoc-Val-OH, **resin 12k**: loading = 0.41 (65%). Found: N, 0.6; S, 4.8.

For Fmoc-Pro-OH, **resin 12l**: loading = 0.41 (57%). Found: N, 0.7; S, 4.6.

Dithiane Deprotection of 12h−l Using Periodic Acid (13h−l). Deprotection was carried out following the same protocol outlined for resin **7a−g**.

Resin 13h. Found: S, 1.2 (74%, i.e., 0.51 mmol/g of **13h**).

Resin 13i. Found: N, 0.9; S, 1.1 (75%, i.e., 0.50 mmol/g of **13i**).

Resin 13j: Fmoc analysis 0.50 mmol/g. Found: N, 1.0; S, 1.0 (74%, i.e., 0.45 mmol/g of **13j**).

Resin 13k: Fmoc analysis 0.35 mmol/g. Found: N, 0.3; S, 0.3 (89%, i.e., 0.38 mmol/g of **13k**).

Resin 13l: Fmoc analysis 0.46 mmol/g. Found: N, 0.3; S, 0.3 (89%, i.e., 0.38 mmol/g of **13l**).

Photolysis of Benzoyl Resins (14h,i). Resin-bound benzoyl ester or resin-bound 4-nitrobenzoyl ester (20 mg) and 3,5-dimethoxyphenol (internal standard, 3 mg) in 3:1 distilled THF/MeOH (12 mL) in a quartz test tube were purged with a stream of nitrogen gas for 10 min. The suspension was UV irradiated for 2 h with constant N_2 bubbling to yield the benzofuranyl resin and benzoic acid or 4-nitrobenzoic acid in solution. Twenty-five microliters of solution was removed at various time intervals and analyzed by HPLC using UV detection at 230 nm.

Photolysis of resins **13j−l** was carried out according to the General Photolysis Procedure (**14j−l**).

Resin 14j: Fmoc analysis 0.04 mmol/g.

Resin 14k: Fmoc analysis 0.08 mmol/g.

Resin 14l: Fmoc analysis 0.15 mmol/g.

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Supporting Information Available: Experimental procedures and characterization details for 3-hydroxy-5-methoxybenzaldehyde, 2-(4′-methoxyphenyl)-1,3-dithiane and 2-(3′-trifluoromethylphenyl)-1,3-dithiane, gel-phase ^{13}C NMR for Tentagel samples **6g−9g**, IR spectra for **5a−8a**, as well as photorelease profiles of **8g** in 3:1 CH_3CN/H_2O and of **13h** in 3:1 THF/MeOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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