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A Novel Safety-Catch Linker for the Solid-Phase Synthesis of Amides and Esters

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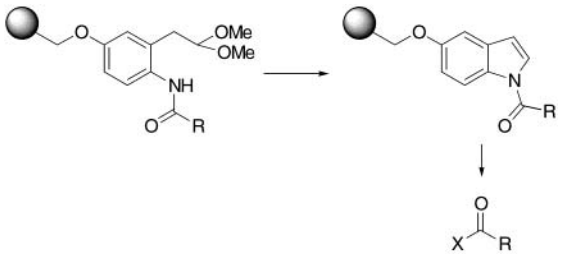
ABSTRACT

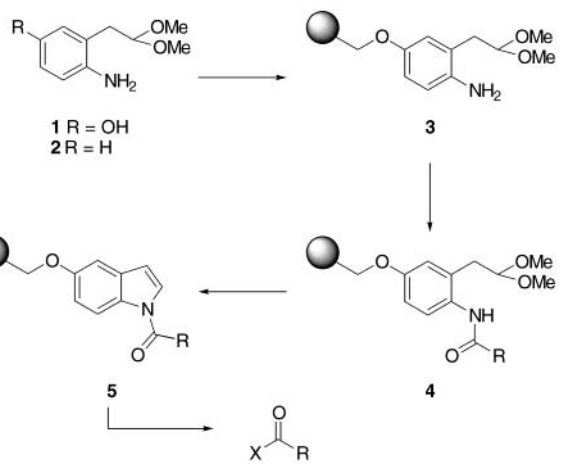


A new safety-catch linker for solid-phase organic synthesis is described. Synthesis and attachment of the linker to the solid phase was achieved via a simple and high-yielding strategy. The linker was exemplified by acylation to form unactivated amides, activation of the linker, and cleavage to release acyl moieties. Acids, amides, or esters were released under mild conditions and with exceptionally high purity. The reactivities of unactivated and activated amides are compared.

Interest in combinatorial chemistry continues to grow, with applications spreading beyond organic synthesis[1] into areas such as materials science[2] and catalysis.[3] This interest drives the development of efficient and reliable chemistry for the solid phase, which in turn requires new strategies of attachment and release of molecules from the solid phase. Safety-catch linkers are a particularly sophisticated form of attachment, whereby a linker present throughout the library assembly in a relatively inert form is activated and thereby made labile at the end of the synthesis to release the products from resin.[4] This paper describes the development of a new safety-catch linker (**1**) for attachment of carboxylic moieties to the solid phase which allows their release as the parent acid or as a simple derivative.

The principle of the linker is that amides such as **4** formed on the aromatic amine will be relatively inert (Scheme 1). However, after treatment with mild acid to remove the dimethyl acetal group, the aldehyde intermediate will rapidly

Scheme 1



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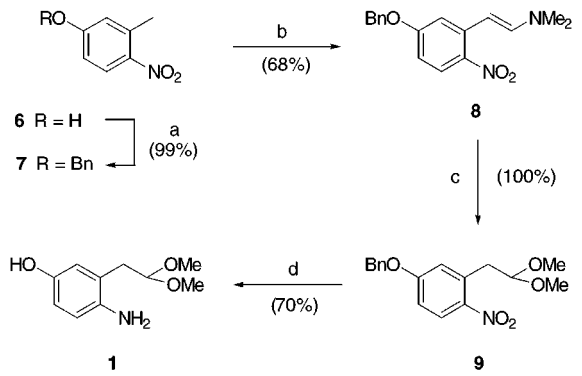
cyclize to form the corresponding acylindole. This amide (**5**) is more reactive and can be cleaved in various ways to yield acids, esters, or amides. Fukuyama et al. have previously reported the use of the dimethyl acetal **2** for the solution-phase protection of acids and synthesis of amides and esters.[5] We have adapted the Fukuyama synthesis of **2** to make **1** where the inclusion of the 5-hydroxy group provides a point of attachment to resin.

The synthesis of dimethyl acetal **1** (Scheme 2) began with 2-nitro-5-methoxytoluene **6**. The first step was to make the benzyl ether **7**. The formation of the enamine **8** then proceeded well[6] and conversion of the enamine to dimethyl acetal **9** was quantitative. If the 4-hydroxyl group was not protected, 2-nitro-5-methoxytoluene was found to be a major side product in the reaction to form the enamine. Catalytic reduction of the nitro group of **9** also removed the benzyl protecting group, to give the final linker **1** in an overall yield of 47% over the four steps.

Scheme 2[a]

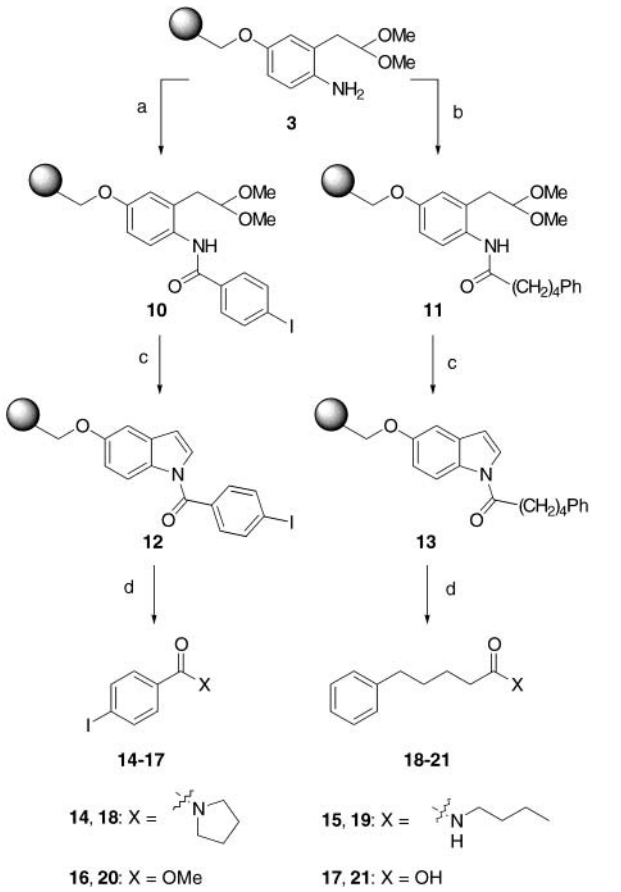


[a] (a) BnBr, Cs_2CO_3, DMF, rt, 16 h; (b) $Me_2NCH(OMe)_2$, DMF, reflux; (c) CSA, MeOH, reflux, 16 h; (d) 10% Pd/C, H_2, EtOH, rt, 2 h.

The linker **1** was then attached to the resin by treatment with sodium methoxide in *N*,*N*-dimethylacetamide (DMA) with tetrabutylammonium iodide at room temperature. This gave quantitative loading as determined by the gel-phase ^{13}C NMR spectrum of the resin **3**. The linker loading was further confirmed by attachment and subsequent cleavage of an *N*-9-fluorenylmethyloxycarbonyl group, and by the observation of expected resin mass gain.

The support-bound linker **3**, which is stable to storage at ambient conditions, was then derivatized with 4-iodobenzoyl chloride or 5-phenylvaleric acid to give resins **10** and **11**, respectively (Scheme 3). IR spectroscopy and the Kaiser test[7] clearly indicated complete acylation of the aniline. The acid-catalyzed closure of the indole ring to give **12** and **13**, respectively, was carried out using PPTS in toluene at 50 °C. This reaction resulted in complete disappearance of the NH stretches and a significant shift of the carbonyl stretches in the IR spectrum. The expected changes were also observed by gel-phase ^{13}C NMR spectroscopy: loss of the benzylic, methoxy, and acetal carbons at 37, 55, and 107 ppm and appearance of two new sp^2 carbon signals of the indole at 104 and 110 ppm, respectively (Figure 1). Quinoline, also reported as a catalyst for this reaction in solution,[5] was found to give no conversion to the indolylamide.

Scheme 3[a]



[a] (a) 4-iodobenzoyl chloride, pyridine, CH_2Cl_2, rt, 16 h; (b) 5-phenylvaleric acid, HATU, pyridine, DMA, rt, 16 h; (c) PPTS, toluene, 50 °C, 16 h: (d) see Table 1.

The activated amides **12** and **13** were studied under a variety of cleavage conditions. Treatment of resin **12** with

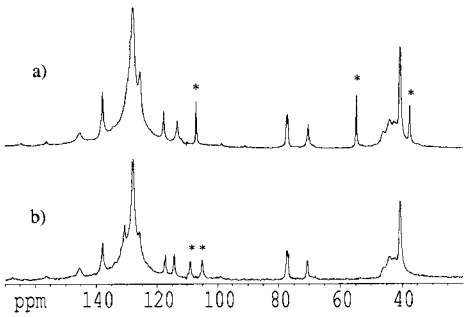


Figure 1. The gel-phase ^{13}C NMR spectra of the linker in (a) its unactivated form **10** and (b) the ring-closed, activated form **12**. Peaks marked with an asterisk in (a) are lost on ring closure and in (b) are the newly formed indole peaks.

excess *n*-butylamine in THF at room temperature resulted in release of butyl-*p*-iodobenzamide **15**. After shaking the resin overnight, this product was obtained in 70% yield. Most encouragingly, however, the released product was greater than 98% pure by HPLC and by proton NMR spectroscopy. Conditions were optimized for the production of amides, esters, and acids (Table 1). In all of the amide releases undertaken, around 50% of product was liberated after 3 h, 70% after 16 h, and 90% after 72 h. Yields are quoted for the four-step procedure on the basis of the initial loading of the Merrifield resin. The reaction was found to be solvent sensitive, product release in toluene was more sluggish than in THF, and the reaction required elevated temperatures.

Table 1. Yields and Purities of Cleaved Products

product	% yield (time)	% purity[d]
14[a]	96 (72 h)	>95
15[a]	90 (72 h)	>95
16[a]	89 (0.5 h)	>95
17[a]	91 (16 h)	>95
18[b]	92 (72 h)	>98
19[c]	89 (72 h)	>98
20[b]	94 (0.5 h)	>98
21[c]	58 (16 h)	93
24[a]	84 (72 h)	>95
25[b]	92 (0.5 h)	>98

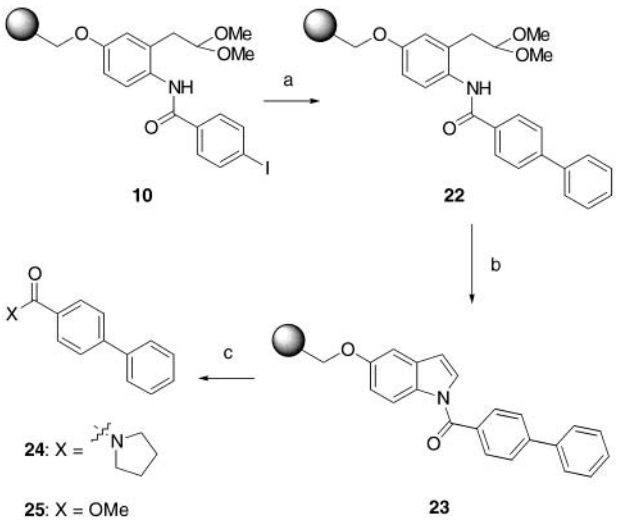
[a] 15 equiv of amine, THF, rt, wash cleavage mixture with 1 N HCl. [b] 5% MeOH in THF, catalytic $NaNH_2$, wash cleavage mixture with saturated NH_4Cl. [c] 1:1:3 1 N NaOH:MeOH:1,4-dioxane. [d] All cleaved products except **21** were >99% pure by HPLC with UV detection (254 nm); >95% indicates trace impurities by ^1H NMR spectroscopy; >98% indicates no impurities by ^1H NMR spectroscopy.

Methyl ester production was carried out with 5% methanol in THF with a catalytic amount of sodium amide. By employing this system, a wider range of ester products should be accessible from this linker since one is not limited to alcohols which swell Merrifield resin.

In all cases purities and yields were excellent. No purification of the product was required beyond aqueous washing of the cleaved material. When the unactivated dimethyl acetal resins **10** and **11** were treated under the optimized conditions for amide release from **12** and **13**, respectively, only traces of product were observed. Under such conditions, resin **12** was shown to be around 400 times more labile than **10**.[8]

A Suzuki cross coupling reaction was carried out on resin **10** to exemplify the utility of this linker (Scheme 4). Reaction with phenylboronic acid in the presence of palladium(0) gave the biaryl resin **22**. No decomposition of the linker or indole formation was observed by gel-phase ^{13}C NMR spectroscopy during this step**.** Dimethyl acetal **22** was then ring-closed to **23** prior to cleavage with pyrrolidine or methanol to yield biaryls **24** and **25**, respectively. Again, yields and purities were excellent (Table 1), with no need for chromatographic purification.

Scheme 4[a]



[a] (a) $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, DMF, 50 °C, 16 h; (b) PPTS, toluene, 50 °C, 16 h; (c) see Table 1.

In summary, we have shown the facile attachment to the solid phase of the novel safety-catch linker element **1** which may be used in the generation of carboxylic acids, esters, and amides. Release is effective under extremely mild conditions, and purities and yields are exceptional in all cases studied. It is envisaged that this linker will have wide utility in solid-phase organic synthesis.

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Supporting Information Available: Experimental details of resin preparations and cleavages. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Determined using an internal standard in the ^1H NMR spectra of two identically trreated batches of **12** and **10**.