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Target alcohol/phenol release by cyclative cleavage using glycine as a safety catch linker†‡

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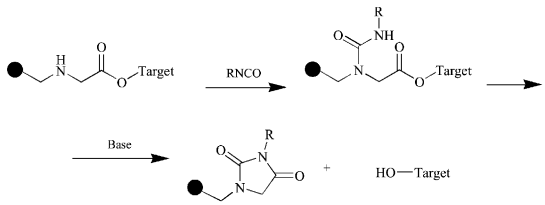
The utility of glycine as a safety catch linker for the immobilization of alcohols and phenols to the solid-support is demonstrated by performing a variety of synthetic transformations.

The synthesis of small organic molecules on solid-support has received widespread attention.[1] The repertoire of organic reactions developed on the solid-phase is considerable and paramount to the synthesis of compound libraries on solid-support is the availability of suitable linkers for attachment of the desired compounds to the polymeric carrier. Linkers[2] that are broadly applicable, stable under the variety of reaction conditions used for elaborating the substrate and yet allow release of the synthesized products under mild conditions are highly desirable. The key challenge in the design of new linkers is to utilize cleavage reagents which can be easily removed from the released products and thus facilitate automation.

Not surprisingly, given the range of reaction conditions a linker may have to survive, the different types of molecules and functional groups that may have to survive the cleavage conditions and the wide variety of functional groups through which a substrate may be attached to the solid-phase, a wide variety of linkers have been designed and synthesized. Safety catch linkers rely on a two step cleavage process.[2a,3] The first step involves activation of the linker and the second step involves the actual cleavage. The main advantage of safety catch linkers is that conditions similar to the cleavage conditions can be accommodated during the synthesis, as the linker is stable until activated. Cyclative cleavage occurs when reagent treatment induces a pendant functionality to attack the product resulting in cleavage from the solid-support. Cyclative cleavage is highly desirable especially for preparing libraries since products can be isolated in high purity avoiding the need for purification. Only those molecules containing the nucleophile would undergo cleavage, hence if synthetic steps which introduced the nucleophile went in poor conversion, the desired product would be mainly obtained after cleavage although in poorer yields.[4] We now report on the development of glycine as a new safety catch linker,[5] that permits anchoring and release of alcohols and phenols from the polymeric support in high yield under mild conditions. The key mechanistic feature of the safety catch linker is product release by cyclative cleavage *via* hydantoin formation on the solid-support. Activation of the linker, involves reaction with an isocyanate to afford a urea, which upon treatment with a base undergoes cyclization releasing the target alcohol (Scheme 1).

The glycine ester **3a** was prepared by coupling commercially available aminomethyl polystyrene **1** with iodoacetate **2**, elaborated by esterification of chloroacetic acid with piperonyl alcohol followed by the Finkelstein reaction. Activation of **3a** with benzyl isocyanate and subsequent treatment of the resulting urea **4** with neat diisopropylamine[6] releases piperonyl alcohol in 80% yield (Scheme 2). This experiment clearly

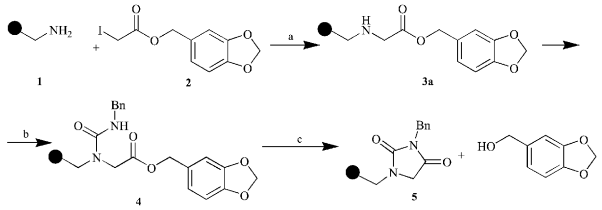


Scheme 1

demonstrates the utility of the linker to release alcohols[7] under mild conditions and in high yield.

The suitability of the linker for application in a variety of synthetic transformations was then investigated. Towards this end, *tert*-butyl glycine·HCl was coupled[7] to Merrifield resin in the presence of NaI at 65 °C for 36 h using Hunig's base and DMF as the solvent to afford **3b**. Deprotection with 1:1 TFA–DCM and rinsing with 5% Et_3N–DCM afforded acid **6**, which was esterified with *p*-iodobenzyl alcohol. The polymer bound aryl iodide **3c** was then transformed by Suzuki[8] and Sonogashira[9] reactions (Scheme 3). The products **8** and **10**, respectively, were released from the solid-support under mild conditions employing the two step activation and cyclization protocol.[7] In another experiment, the polymer bound glycine **6** was esterified with methyl-3-OH-cinnamate. The unsaturated ester **3d** so obtained was subjected to nitrile oxide cycloaddition[10] to afford a 4:1 mixture of regioisomeric products **13** and **14** in high yield and purity after cleavage from solid support[7] (Scheme 3). Furthermore, glycine **6** was esterified with hydroquinone and the resulting product, **3e** was subsequently reacted with *p*-iodobenzyl alcohol employing the Mitsunobu protocol to afford the ether **15**. Cleavage from solid-support afforded product **16** in 60% yield[7] (Scheme 3). It is important to note that the presence of the free amino group in the linker imposes restrictions on the reactions that can be performed. For instance, acylation of the hydroxy group in the product, or use of oxidants like peroxides and peracids. By virtue of the alcohol being attached to the linker by an ester linkage, reducing agents need to be avoided. Acidic conditions would quaternise the amine, however treatment with a tertiary amine would regenerate the linker. The protection of the amino group as a carbamate (Fmoc) would however remedy these deficiencies.

To conclude, a new safety catch linker for immobilizing alcohols and phenols that is stable under a wide variety of reaction conditions and yet cleaved under mild conditions has been developed. The alcohol that is to be immobilized can either be reacted directly with the glycine linker **6** using DCC or be



Scheme 2 *Reagents*: (a) iPr_2NEt, DMF, rt, 16 h; (b) $PhCH_2NCO$, toluene–DMF (1:1), rt, 8 h; (c) iPr_2NH, rt, 1 h 80%.

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‡ Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b2/b203270h/

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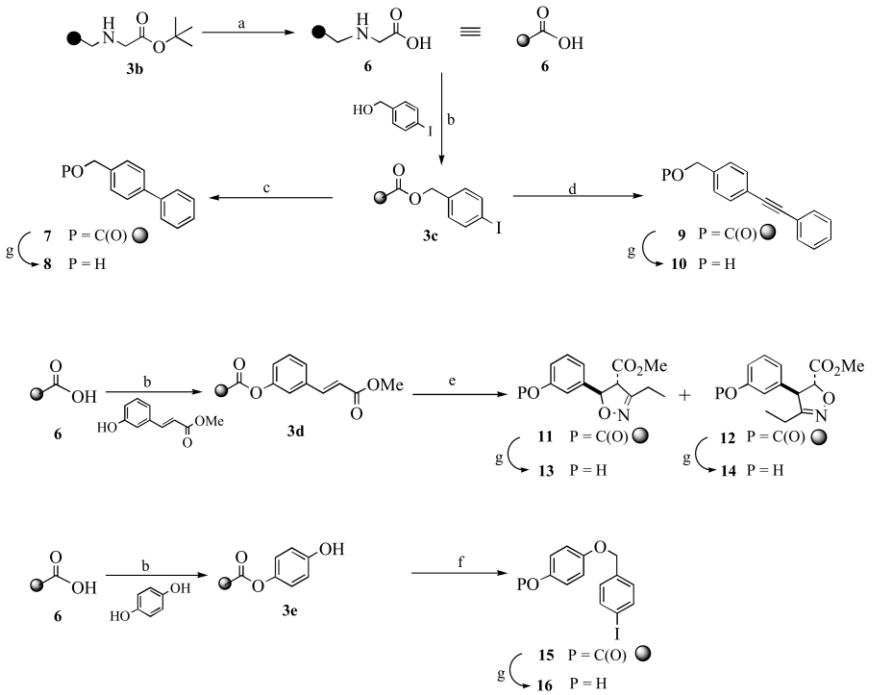

Scheme 3 *Reagents*: (a) TFA–DCM (1 : 1), rt, 3 h; (b) DCC, HOBT, Cat. DMAP, DCM, rt, 8 h; (c) $Pd(OAc)_2$, $PhB(OH)_2$, K_2CO_3, dioxane–H_2O (7 : 1), 100 °C, 24 h; (d) $PdCl_2(PPh_3)_2$, CuI, Et_3N, dioxane, rt, 24 h; (e) $PrNO_2$, 4-OMe-PhNCO, Cat. Et_3N, PhH, rt, 16 h (f) DEAD, PPh_3, THF, rt, 16 h; (g) (i) $PhCH_2NCO$, toluene–DMF (1 : 1), rt, 8 h, (ii) iPr_2NH, rt, 1 h, **8** = 70%, **10** = 72%, **13** + **14** = 70%, **16** = 60%.

esterified in solution as the iodoacetyl ester and then be immobilised by an alkylation reaction to the aminomethylpolystyrene **1**. The conditions for activation and cleavage are especially mild and the products are obtained in high yield and purity. Moreover, the cleavage reagent employed makes the linker suitable for automation.

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