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# Resin-bound 4-phenyl-1,2-dihydroquinoline (DHQ): a new safety-catch linker for solid-phase organic synthesis (SPOS)

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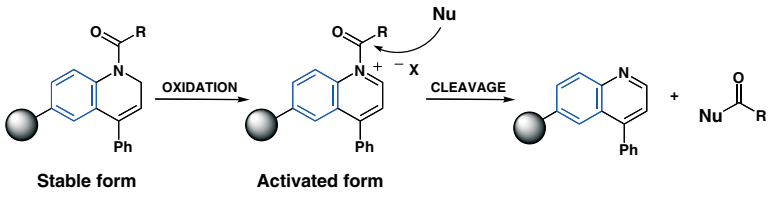
**Abstract**—A new safety-catch linker has been developed for combinatorial solid-phase chemistry. Azidomethyl-polystyrene, obtained by nucleophilic substitution of chloromethyl-polystyrene, undergoes an acid promoted Schmidt rearrangement. The resulting polymer-bound iminium participates in an aza Diels–Alder cycloaddition, which leads to a supported dihydroquinoline (DHQ resin). The acylated form of the DHQ resin is stable under basic, acidic and mild reducing agents. The cleavage proceeds in two steps (i) oxidative aromatization leading to an activated quinolinium and (ii) nucleophilic displacement of the quinoline resin. The overall process is high yielding and efficient.


Due to the recent emergence of combinatorial chemistry, first for the synthesis of peptides and nucleotides,[1,2] then for the discovery and optimization of pharmaceutical lead molecules,[3,4] there has been tremendous attention given to the development of efficient linkers.[5–9] An ideal linker would fulfill a number of important criteria. First, the attachment of the starting material has to be achieved in high yield. Second, the linker must be stable to the chemistry used in the synthesis. Third, the cleavage must be efficient under conditions that do not damage the final product or introduce impurities that are difficult to remove during the workup. Finally, it needs to be readily available and inexpensive.

Among others, safety-catch linkers appear to be particularly attractive as they are stable until activated. In fact, the release of the final target compounds rely on a two-step process. The first involves activation of the linker, while the second involves the actual cleavage.

As part of an ongoing project on developing new solid-phase linkers and synthetic schemes for SPOS, we focused our attention on the development of a novel *N*-acyl dihydroquinoline/*N*-acyl quinolinium-switch based safety-catch linker (Scheme 1).

Analogous linkers have already been reported, but their preparation remains laborious. Indeed in many cases, the linker is prepared in solution phase before being attached to the solid support.[10] This method allows access to high loadings but often requires a lengthy and tedious multi-step synthesis of the linker precursor.




**Scheme 1.** *N*-Acetyl dihydroquinoline/*N*-acetyl quinolinium-switch based safety-catch linker.

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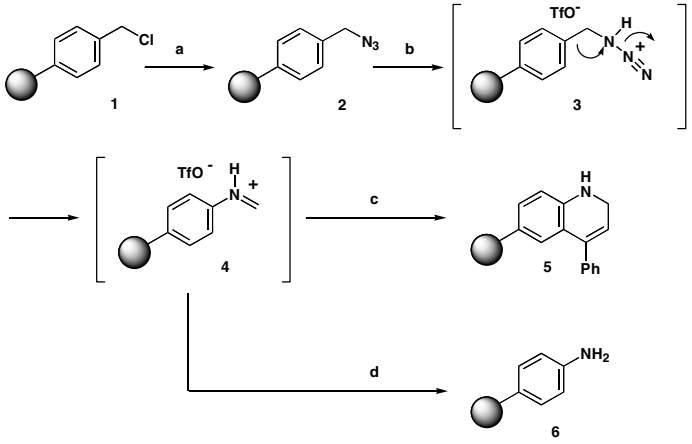
In a previous paper,[11] we described a straightforward preparation of a new amino-polystyrene resin in a two-step process starting from readily available Merrifield resin. The synthesis relied on the hydrolysis of a transient resin-bound iminium intermediate formed through a one-carbon degradative Schmidt rearrangement. Herein we report the synthesis of supported 1,2-dihydroquinoline, a novel new safety-catch linker, through an aza-Diels–Alder reaction of the same transient resin-bound iminium intermediate with phenylacetylene (Scheme 2).

Each step was monitored using IR spectroscopy (recorded using a Perkin–Elmer 2000 FT-IR directly on the resin beads). The solid-phase synthesis was initiated by treating commercially available Merrifield resin (chloromethylated polystyrene, 1% cross-linked divinylbenzene, 1.58 mmol $g^{-1}$) with sodium azide and a small amount of sodium iodide in DMF, and heating at 90 °C, to afford the benzyl azide resin **2** ($\nu_{N=N=N} = 2095\ cm^{-1}$) in excellent yield (>95% determined by elementary analysis of the nitrogen; loading = 1.56 mmol $g^{-1}$).

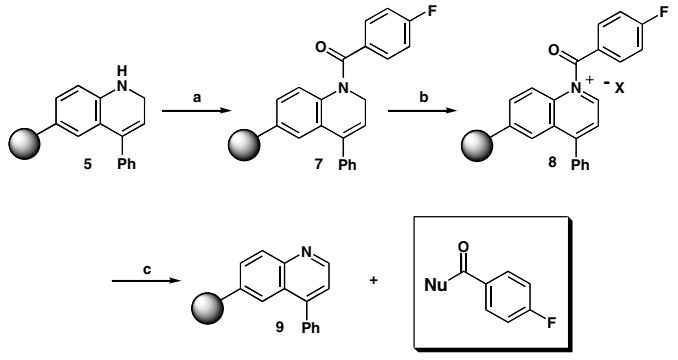
Resin **2** was then subjected to an acid-promoted Schmidt rearrangement under conditions adapted from Aubé[12] and Pearson[13] as previously reported.[11] Treatment of a suspension of **2** (1 g) in $CH_2Cl_2$ (10 mL) with triflic acid (1.4 mL) at 0 °C for 1 h promoted the 1,2-polymer migration with concomitant liberation of molecular nitrogen leading to the formation of the phenyl-iminium intermediate **4**. Phenylacetylene (1.4 mL) was then added to produce the desired supported 4-phenyl-1,2-dihydroquinoline **5** in high yield (>95% as determined by fluorine elementary analysis of the corresponding resin prepared using 1-ethynyl-4-fluorobenzene, loading = 1.20 mmol $g^{-1}$).

The use of resin **5** as a new safety-catch linker for solid-phase organic synthesis was then investigated (Scheme 3). Treatment of the resulting resin with 4-fluorobenzoyl chloride and triethylamine in $CH_2Cl_2$ at 0 °C afforded resin **7** in 88% yield (loading = 0.94 mmol $g^{-1}$) as determined by fluorine elementary analysis.

The resulting amide bond was shown to be stable under either basic or acidic hydrolytic conditions. Indeed, it was not hydrolyzed upon treatment with 1 M HCl or NaOH in THF–$H_2O$ solution over 24 h. Moreover, it also proved to be stable under Boc/Fmoc deprotecting conditions (20% TFA in $CH_2Cl_2$ and 20% piperidine in




**Scheme 2.** Reagents and conditions: (a) 4 equiv $NaN_3$, NaI, DMF, 90 °C, quant.; (b) 4 equiv TfOH, $CH_2Cl_2$, 0 °C to rt; (c) 4 equiv PhC≡CH, rt, >95% (two steps); (d) MeOH/$H_2O$, rt (see Ref. 11) >95%.




**Scheme 3.** Reagents and conditions: (a) 4 equiv (*p*-F)PhCOCl, 10 equiv $NEt_3$, $CH_2Cl_2$, 0 °C, 88%; (b) oxidation using DDQ, CAN or $CPh_3BF_4$, rt; (c) cleavage with a nucleophile at rt, 34–98% yield over two runs.

**Table 1.** Cleavage conditions

| Entry | Reagent | Solvent (temperature) | Yield[a] (%) |
|---|---|---|---|
| 1 | DDQ | $CH_2Cl_2/CH_3CN$ (rt) | 34 |
| 2 | $CPh_3BF_4$ | THF (rt) | 42 |
| 3 | $CPh_3BF_4$ | $CH_2Cl_2$ (rt) | 59 (96[b]) |
| 4 | CAN | $CH_3CN/H_2O$ (rt) | 62 (98[b]) |

[a] Yield of the cleavage sequence determined by quantification of the recovered product.
[b] Cumulated yield after two-activation/cleavage sequences.

DMF; 24–60 °C), and reducing conditions such as $NaBH_4$ in MeOH.

The activation of the resin–substrate bond was performed using various oxidizing reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), ceric ammonium nitrate (CAN) and triphenylcarbenium tetrafluoroborate ($CPh_3BF_4$). Cleavage of the amide bond was then possible using a nucleophile such as benzylamine (entries 1–3) or water in the case of CAN (entry 4). The efficiency of the activation–cleavage sequence was determined by quantification of the recovered product. The results are depicted in Table 1.

In the case of DDQ and $CPh_3BF_4$, resin **7** was treated with 3 equiv of the desired oxidizing reagent at room temperature for 10 and 3 h, respectively, to promote the formation of the *N*-acyl quinolinium species **8**. The resulting resin was filtered and treated with an excess of benzylamine in $CH_2Cl_2$. After filtration and thorough washing with MeOH and $CH_2Cl_2$, the organic solvents were combined and evaporated under vacuum to afford a mixture of the desired amide along with the excess of benzylamine. Quick filtration through a cartridge of silica afforded the amide in 34% and 59% isolated yields, respectively.

Cleavage using CAN was performed in 'one pot' using a mixture of $CH_3CN/H_2O$ at room temperature. 4-Fluorobenzoic acid was recovered in 62% yield without any purification needed.

In all four experiments, infra-red spectroscopy of the beads showed a stretch at 1651 $cm^{-1}$ ($\nu_{CO}$) indicative of an incomplete cleavage. A second sequence using $CPh_3BF_4/CH_2Cl_2$ or $CAN/CH_3CN/H_2O$ led to the total cleavage of the amide bond. In addition, the purity of the recovered material was over 95% as determined by $^1H$ NMR spectroscopy.

In conclusion, we have developed a new safety-catch linker for solid-phase chemistry. This new linker is stable under Boc and Fmoc deprotecting conditions, can be prepared in both large quantities and high purity, and is cleaved under mild oxidative conditions. Finally, as the excess of oxidizing reagents is removed by filtration after the activation step, no impurities are introduced during the cleavage.

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