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Ethynyldiisopropylsilyl: A New Alkynylsilane Protecting Group and "Click" Linker

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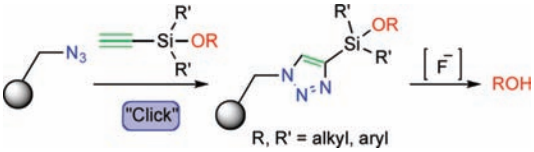
ABSTRACT



A new silyl-based reagent has been developed for "catch and release" immobilization, combining click chemistry with silyl protection. The traditional "all carbon" attachment to solid supports in a silyl type linker was substituted with a stable triazole, easily assembled using the CuAAC reaction. The methodology introduces a novel ethynyldiiospropylchlorosilane reagent (EDIPS-Cl) as a functionalized protecting group linker.

Solid phase synthesis (SPS) has proven to be a powerful tool in organic chemistry. This revolutionary technology has enabled significant achievements in the fields of total synthesis,[1] split-pool synthesis,[2] high-throughput screening,[3] combinatorial chemistry,[4] diversity oriented synthesis,[5] and more recently supported reagents for flow chemistry.[6]

One of the key challenges in SPS involves immobilizing the substrates (or reagents) onto the solid support, thus driving the demand for the development of new and innovative linkers.[7] The ideal linker should be robust and able to withstand a wide variety of reaction conditions, yet should be readily cleaved under mild, chemoselective conditions that do not degrade the products.[7] For example, silyl linkers, which are commonly used to attach alcohol-containing substrates, have proven highly valuable owing to their inertness to a wide range of synthetic transformations, yet are easily removed under selective conditions.

The so-called "all carbon backbone silyl linkers",[8] such as diisopropyl **1**,[9] *n*-alkyldiisopropyl linker **2**,[10] and the recently introduced TBDAS-type silyl linker **3**[8] (Figure 1) are common. In such examples, the silane is generally first attached to the resin followed by loading of the substrate. Reactions such as lithiation of polystyrene followed by trapping of the aryllithium intermediates with dialkyldichlo-

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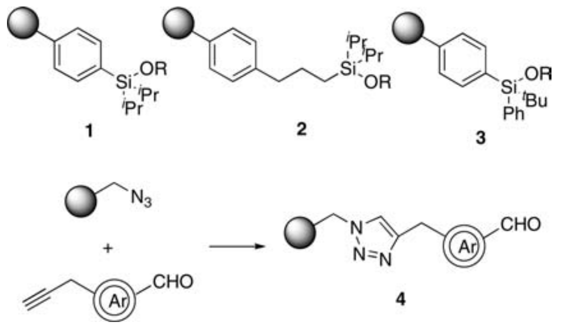


Figure 1. Silyl ethers and triazole linkers.

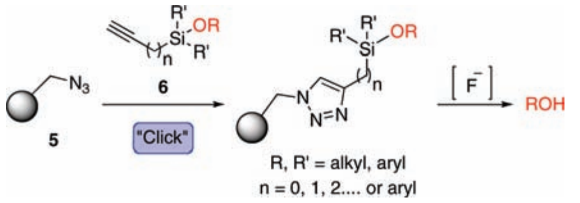
rosilanes[9,11,12] and hydrosilylation of resin bound olefins[13] followed by the activation of the silyl hydride with triflic acid,[14] trichloroisocyanuric acid,[10] or 1,3-dichloro-5,5-dimethylhydantoin[13] are widely employed. The target resin-bound silyl ethers are then formed in situ by loading the corresponding alcohol.[8−10] The given cleavage conditions depend upon the nature of the substituent but generally involve fluoride sources or protic reagents.[8,13]

Though a number of versatile silyl linkers are described in the literature,[7] our interest in click chemistry[15] and in particular the CuAAC reaction[16] prompted us to design and develop a complementary linker strategy. Our bifunctional reagent would comprise a silyl core capable of reversibly “tagging” a functional group, such as an alcohol and an orthogonally reactive functional handle such as an alkyne, ready for “capture” onto a solid phase.

Click chemistry has found previous application in SPS, with the corresponding triazole “linker” functionality being ideal due to its robust nature and inertness to a wide range of conditions. Gmeiner et al. have reported a modified BAL (Backbone Amide Linker),[17] which involved reacting the azido polystyrene with an appropriately laced alkyne substrate. Cleavage of the amide group was achived by TFA with loss of the aryl spacer group. The key to the success of this methodology was the introduction of a suitable terminal alkyne into the substrates for the 1,3-dipolar cycloaddition (**4**, Figure 1).

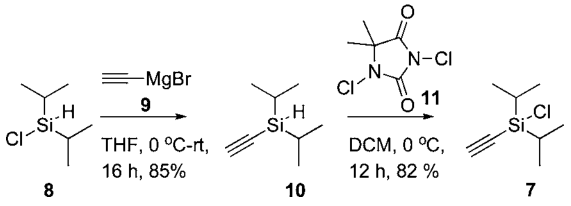
Herein, we report a new catch and release click linker, designed to facilitate mild loading and cleavage. We envisioned that an azide-functionalized resin **5** and alkynylsilane-protected substrate **6** would be suitable partners for this purpose (Scheme 1). The azido-functionalized resin could readily be obtained from Merrifield resin upon treatment with sodium azide,[18] whereas the proposed ethynyldialkylchlorosilane could in principle function as a silyl protecting group, with the alkyne handle serving to immobilize the substrate to the solid phase via CuAAC. The overall design circumvents the need to introduce the alkyne functionality just before loading. In addition, the characteristic IR azide stretch (2100 cm^{-1}) provides a convenient mode to monitor the progress of resin loading.

Scheme 1. “Click” Linker Design



Ethynyldiisopropylchlorosilane (EDIPS-Cl) (**7**) was chosen as the first-generation alkynylchlorosilane for our investigation. Silyl chloride **7** was readily prepared by treating commercially available chlorodiisopropylsilane **8** with ethynylmagnesium bromide **9**,[19] affording **10**, which upon treatment with 1,3-dichloro-5,5-dimethylhydantoin (**11**) gave target **7** (Scheme 2).[13] The chlorination reaction was followed using IR spectroscopy, which showed disappearance of the distinctive Si−H stretch at 2100−2200 cm^{-1}.

Scheme 2. Synthesis of **7**



Reagent **7** proved a good choice and could be reacted with the hydroxyl group of several diverse substrates including secondary, benzylic, and allylic alcohols, to give their corresponding EDIPS protected silyl ethers **12**−**17**, in good to excellent yields (Scheme 3). Optimal conditions were found with DCM as solvent, Et$_3$N as base, and a catalytic

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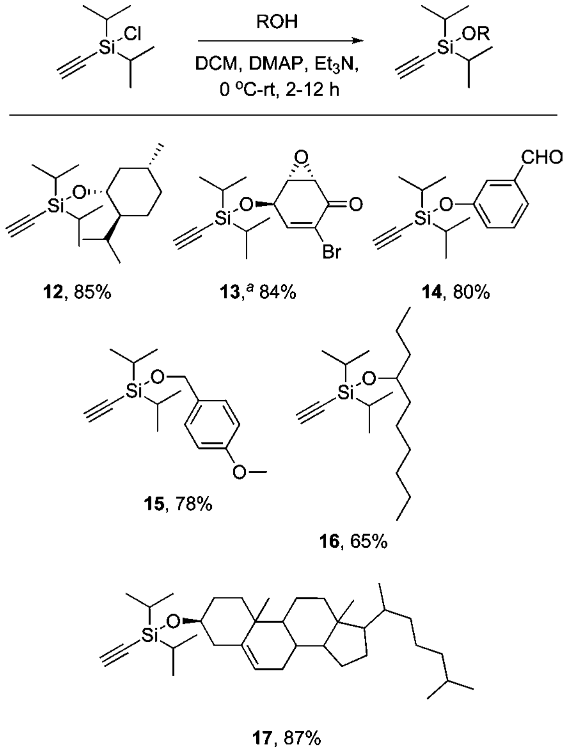
quantity of DMAP. The successful formation of **7** was pleasing since the functionalized silanes not only served to protect the alcohol moiety but at the same time offered a handle for “capturing”.

Scheme 3. Synthesis of Ethynyldiisopropylsilyl (EDIPS) Protected Alcohols



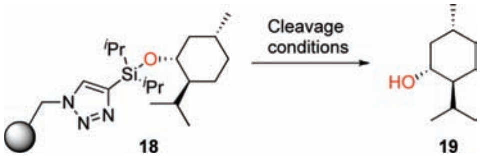
[a] 2,6-lutidene was employed as a base.

The solid phase investigation began by loading silyl-protected menthol **12** onto the azidomethyl polystyrene (**5**) using the conditions of Gmeiner et al. (Cu(I), DIPEA in 1:1 THF:DMF).[17] The reaction was followed by filtering the resin and extensive washing with Py, MeOH, THF, and DCM. The resin was dried under high vacuum to afford the triazole linked substrate. The positive increase in the weight of resin after the reaction indicated successful loading (70%).

Cleavage conditions were next investigated, screening with both protic and fluoride sources (Table 1). HF•pyridine[8] at room temperature gave the best results. The liberated alcohols were recovered after removal of excess cleavage reagent by addition of methoxytrimethylsilane and evaporation of residual solvent. Passing the residue through a plug of silica gel afforded pure products which were identified by ^{1}H NMR spectroscopy. Though TBAF also led to substrate cleavage, the yields were comparatively low. On the other hand, a 6:6:1 acetic acid:THF:H_2O system[13] effected smooth cleavage in moderate yields, thereby providing an alternative to the HF•pyridine system.

To test the scope of the protocol, the variously substituted aryl, alkyl, and vinyl alcohols (Scheme 3) were loaded onto the resin and subsequently cleaved. The results are summarized in Table 2. Gratifyingly, all entries showed good to moderate loading and cleavage, thereby proving the generality of the protocol.

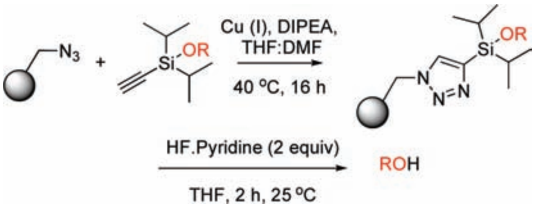
Table 1. Optimization of Solid Phase Silyl Cleavage



entry	reagents (2 equiv)	temp (°C)	time	cleavage[a]
1	HF•pyridine	25	2 h	72%
2	TBAF, THF	25	2 h	16%
3	NH_4F, THF	25	2 h	9%
4	6:6:1 AcOH:THF:H_2O	25	2 days	44%

[a] Percent cleavage was determined by the weight of the isolated product after passing through a plug of silica gel.

Table 2. Loading and Cleavage of **12**−**17**



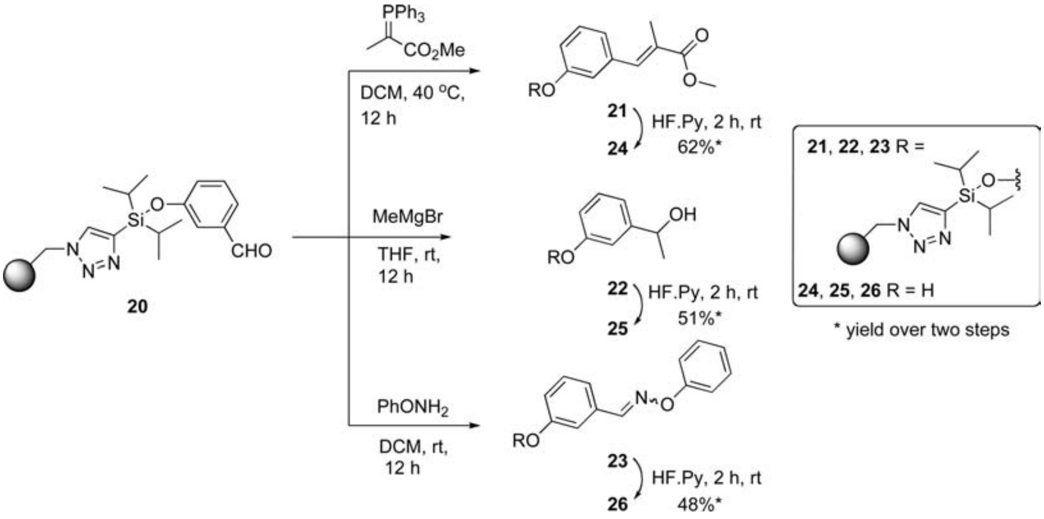
entry	substrate	loading[a]	cleavage[b]
1	**12**	70%	72%
2	**13**	45%	65%
3	**14**	76%	85%
4	**15**	75%	80%
5	**16**	65%	60%
6	**17**	73%	78%

[a] Loading was estimated based on an increase in weight of the resin. [b] Percent cleavage was determined by weight of the isolated compound after passing through a plug of silica gel.

To demonstrate the inertness of the silyl “click” linker, representative reactions on aldehyde **20** were performed on the solid phase. As illustrated in Scheme 4, the resin bound aldehyde **20** could be converted to the (*E*)-alkene **21** via Wittig olefination or to the secondary alcohol **22** via methyl Grignard addition, whereas oxime formation **23** was observed on reaction with *o*-benzhydroxylamine. HF•Py-mediated cleavage provided the liberated (*E*)-alkene **24** in 62%, the alcohol **25** in 51%, and the oxime **26** in 48% overall yield, respectively.

In conclusion, we have developed a new alkynylsilane reagent (EDIPS-Cl) which functions as a hydroxyl protecting group, equipped with an alkyne handle for a catch and release strategy. We have shown that protected substrates can be readily loaded onto a solid support via a triazole linkage using

Scheme 4. Representative Reactions on **20** and Subsequent Cleavage



the CuAAC reaction and that the corresponding linker is stable to a variety of reaction conditions and chemical transformations. Monitoring of sample loading is made simple by examination of the distinctive azide stretch (2100 cm^{-1}) in the IR spectrum. Subsequent cleavage of the corresponding substrates was readily achieved under mild conditions. We believe the present linker-functionalized protecting group will find wide application in SPS, drug discovery, affinity chromatography, and related areas, and we are currently exploring the scope of this methodology.

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Supporting Information Available: Experimental procedures and analytical data for **7**, **10**, and **12**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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