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A Linker That Allows Efficient Formation of Aliphatic C-H Bonds on Polymeric Supports

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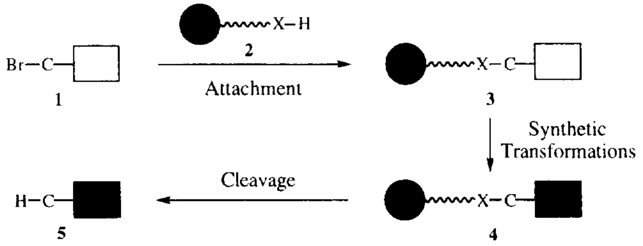
Abstract: *Alkyl group bearing polymer* ***10*** *was prepared by way of sulfide* ***8*** *and thiol* ***11*** *in high yields. Cleavage of the alkyl chain from the PEG polymer support was accomplished either by homolysis under radical conditions or by desulfurization using Raney nickel to yield the new carbon-hydrogen bond product* ***12****. The methodology developed will allow a variety of molecular scaffolds to be readily manipulated on a polymeric matrix.* Copyright © 1996 Elsevier Science Ltd

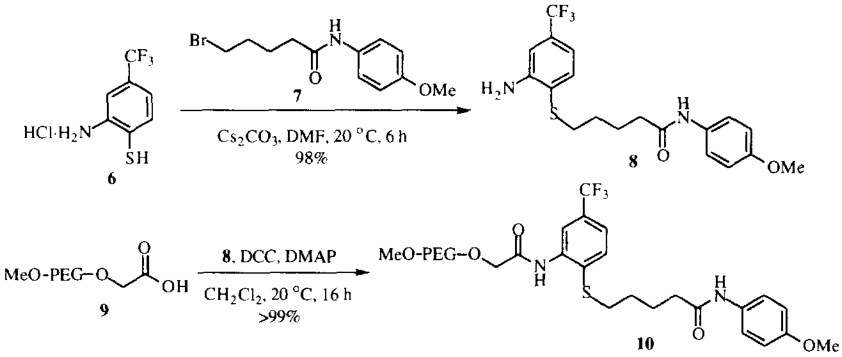
Combinatorial chemistry has been touted as the latest core technology in the drug discovery quest, the premise being that the rapid assimilation of new molecules should greatly facilitate the search for lead compounds and their optimization.[1] Indeed, the preparation of the first non-peptide, small molecule libraries took place four years ago[2] and since that time a rapid development of new chemistries typically adapted to polymeric matrices has evolved.[3] Unheralded, yet crucial to the expansion of combinatorics is the design and synthesis of versatile polymeric linkers containing both facile points of attachment and cleavage.

Scheme I



Vital to all successful solid phase organic methodologies is final liberation of the product from the polymeric support. Typically this step gives rise to the formation of hetero atomhydrogen bonds, yielding functional groups such as alcohols, amines, and amides.[4] Although these afore-mentioned methods are plentiful, new cleavage protocols are required, including ones leading to the formation of carbon-hydrogen bonds. Examples of C-H bond formation exist, however they have been limited to benzylic, aromatic and aldehyde C-H bonds.[5] In this regard, an aliphatic carbon-hydrogen bond would be a highly desirable functionality if it could be strategically placed and later recovered from a polymeric support. A versatile linkage for the generation of an aliphatic carbon-hydrogen bond is detailed herein. The general approach is depicted in Scheme I; a small molecule/molecular scaffolding alkyl bromide (**1**) is ligated to a polymer (**2**), resulting in the formation of **3**, which, in turn can undergo various synthetic transformations to deliver **4**. Cleavage from the polymeric linker would provide the desired molecule **5** containing a new carbon-hydrogen bond.

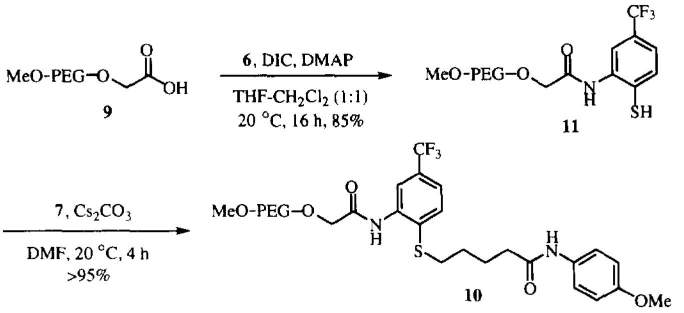
Scheme II



To realize the potential of Scheme I, the following two piece scenario was investigated. Commercially available 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride **6** was examined as a linking unit between the soluble homopolymer MeO-PEG, which we have previously described in Liquid Phase Combinatorial Synthesis (LPCS)[6] and the molecular scaffold. Bromide **7** was selected as the alkylation partner in order to test the feasibility of alkylation and cleavage from **6** (*vide supra*).[7] Smooth alkylation of **6** with bromide **7** and cesium carbonate in a chemospecific manner resulted in the formation of sulfide **8** (Scheme II). Subsequently, sulfide **8** was coupled with polyethylene glycol monomethyl ether carboxylic acid **9** under standard DCC coupling conditions to complete the synthesis of the alkylated MeO-PEG **10**. Evident from this tack are the observed high yields and selectivity. However, the alkyl chain was introduced into the aromatic linker before polymer coupling. Therefore, the generality of this approach is thus somewhat limited. An alternative route that first incorporates the linker into the polymer support followed by its alkylation was next examined.

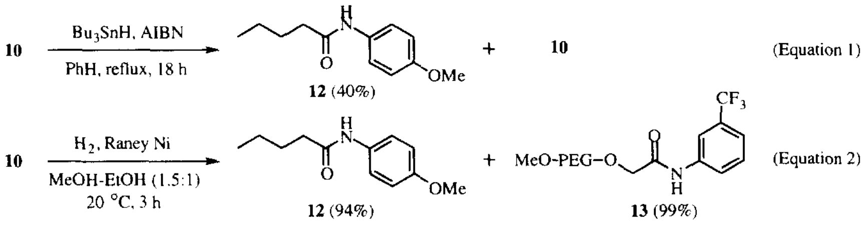
As depicted in Scheme III, the aromatic linker **6** was condensed with MeO-PEG acid **9**, resulting in the MeO-PEG supported thiol **11** which now serves as a general carrier for various alkyl groups. In the coupling reaction, a mixed solvent system (THF-CH_2Cl_2) was employed to enhance the formation of the desired thermodynamically stable amide over the kinetically favored thioester. Interestingly, the exclusive use of CH_2Cl_2 furnished a mixture (*ca.* 1:1) of the two possible coupling products. Alkylation of MeO-PEG thiol **11** was successful in the presence of cesium carbonate in anhydrous dimethylfomamide, the alkylated PEG **10** was obtained in >95% yield.

Scheme III



With the alkylated MeO-PEG in hand, functional group cleavage was examined. Under radical conditions (Bu_3SnH, AIBN),[8] homolysis of the C-S bond occurred at a slow rate. In a typical case, the reaction was cooled to room temperature after reflux for 18 hours, and the solution was triturated with Et_2O[9] to afford precipitated MeO-PEG starting material **10** and the product **12** (equation 1). In contrast, when sulfide **10** was subjected to desulfurization using Raney nickel,[10] the reaction was complete in three hours. Now utilizing precipitation techniques with Et_2O, desulfurized MeO-PEG **13** was obtained quantitatively as a white powder, while the desired alkyl molecule **12** was delivered in a spectroscopically pure form simply by concentration of the filtrate (equation 2). The latter reaction represents a standard methodology for carbon-hydrogen bond formation containing both a facile cleavage method as well as a convenient purification technique.

Scheme IV



In conclusion, the protocol reported allows for a variety of alkyl molecular scaffolds to be incorporated onto a polymeric matrix. In addition, the strategy employed facilitates efficient cleavage of the tethered molecule and the formation of aliphatic carbon-hydrogen bonds. The application to various alkyl groups is now under study, and will be reported in due course.

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