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One-pot esterification-click (CuAAC) and esterification–acetylene coupling (Glaser/Eglinton) for functionalization of Wang polystyrene resin

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ABSTRACT

We report three new sets of one-pot reactions for functionalization of Wang polystyrene resin and its derivatives. We first show that it is possible to combine esterification and CuAAC (Copper-Catalyzed Alkyne-Azide Cycloaddition) in a one-pot reaction with a very high yield. We also demonstrate for the first time that it is possible to combine esterification with either Glaser or Eglinton acetylene-couplings in a one-pot reaction. Finally, we show that the esterification, CuAAC, and Glaser-coupling reactions are all compatible with each other, and it is possible to run in parallel esterification/CuAAC and esterification/Glaser coupling in a single vessel. All reactions are performed at room temperature while the only separation method required is filtering and washing the resin.

Introduction

The use of one-pot reactions for the functionalization of polymers and other purposes has received significant attention.[1,2] By allowing more than one reaction to be performed simultaneously or consecutively in the same vessel, the one-pot method makes it possible to concurrently functionalize polymers with several different groups,[1,2] as well as to synthesize relatively complex structures in a single step, thereby saving both time and effort.[3] It has also been shown that the use of such one-pot reactions can facilitate new growth and polymerization processes.[4,5]

In this Letter we report three new one-pot reactions: (a) esterification–CuAAC (Copper-Catalyzed Alkyne-Azide Cycloaddition); (b) esterification–Glaser coupling and esterification–Eglinton coupling; (c) parallel esterification–CuAAC/esterification–Glaser coupling.

All of the reactions were used to functionalize Wang polystyrene or the first-generation dendronized Wang polystyrene support, and were performed at room temperature with DMF as the solvent, HBTU[6–9] as the esterification reagent, copper(I) iodide as the catalyst/reagent for the CuAAC/Glaser reactions, and DIPEA[10] as the base promoter. The only separation method required, for all cases, was filtration and washing of the resin, making this procedure very simple to carry out.

As far as we know, one-pot esterification–acetylene coupling[10–12] (Glaser[3]/Eglinton[13]), and one-pot esterification/CuAAC/Glaser reactions have not been demonstrated so far in any medium. One-pot esterification–CuAAC (Click)[2] with carboxylic acids has been reported on two occasions.[4,14] However, in both these cases, different reagents were used and the reactions were performed in different mediums.

One-pot esterification-CuAAC (click) reaction

Recently, Shao et al.,[15,16] reported the use of a carboxylic acid, DIPEA, and copper(I) iodide to promote the CuAAC (Click)[2] reaction in non-polar solvents. We noted that these conditions were nearly the same as those used for HBTU-promoted esterification reactions,[6–9] and could be used to combine the esterification and CuAAC reactions in a one-pot method. This method could be very useful for the functionalization of polymers, frequently executed by our group.[17,18] We examined such a reaction using the carboxylic acid both as a promoter for the CuAAC reaction and as a reagent for the esterification reaction (Scheme 1), DIPEA as the base for both reactions, copper(I) iodide as the catalyst for the CuAAC reaction, and HBTU as the reagent for the esterification

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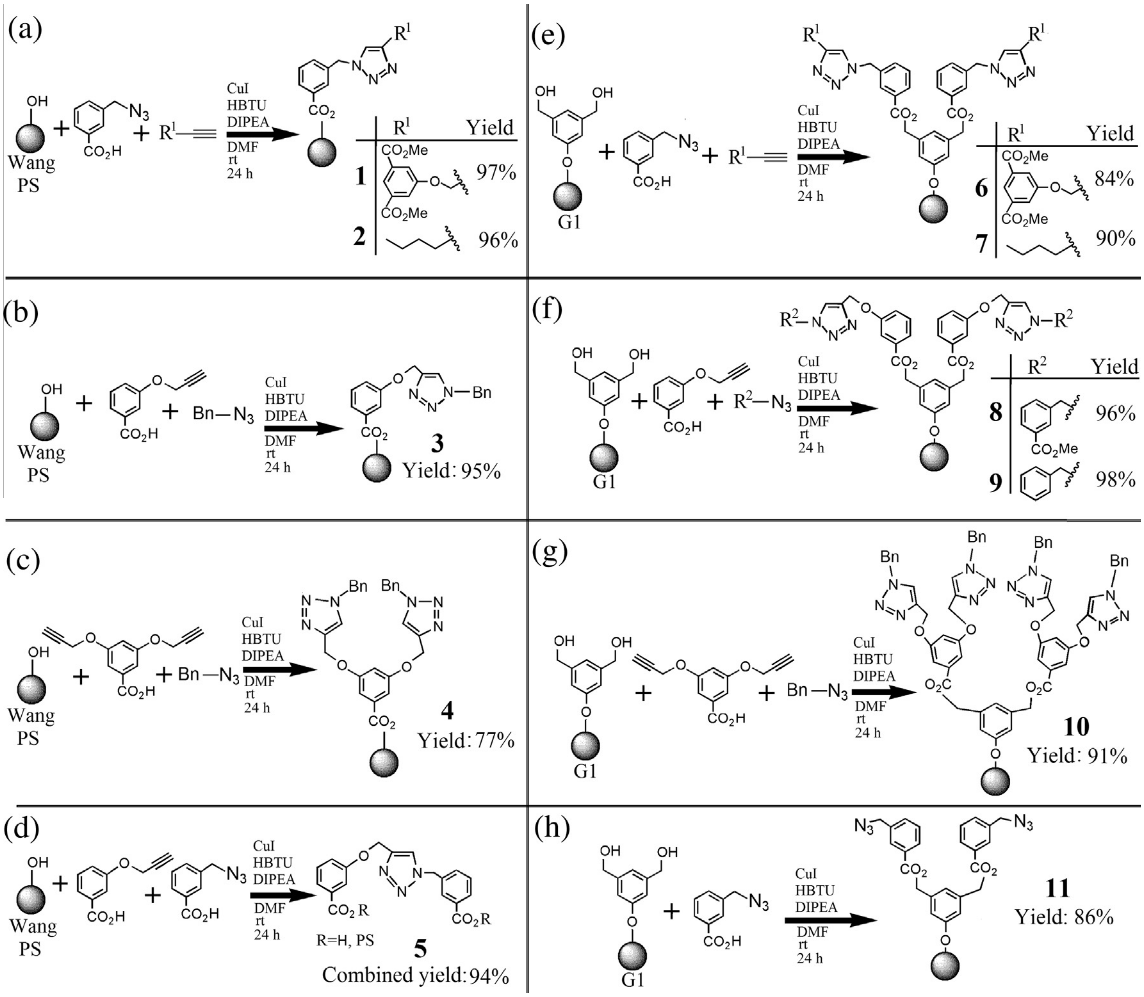

Scheme 1. The esterification-CuAAC one-pot reactions were all performed in a closed vessel, at room temperature for 24 h with DIPEA (0.23 ml), copper(I) iodide (0.079 mmol), HBTU (0.53 mmol), DMF (1 ml), and Wang polystyrene resin (0.89 mmol/g, 0.053 mmol) or G1 resin (0.5 mmol/g, 0.03 mmol). The identity and yield of the products were determined by acidolytic cleavage from the resin, followed by ^{1}H NMR spectroscopy in the cleavage solution with an internal reference (1,1,2,2 tetrachloroethane). PS = Polystyrene. G1 is a first-generation dendronized Wang PS. Reaction d produces two products on the resin; however, once cleaved from the resin both products converge to a single species. Hence, the yield measured by NMR in the cleavage solution is a combined yield of the two products.

reaction. The reaction was performed on Wang polystyrene resin or on the first-generation dendronized Wang polystyrene (G1, Scheme 1 reactions e–h),[17,18] with both carrying free OH groups, as the alcohol reactant, with a carboxylic acid functionalized with an azide or alkyne as the second reactant, and an alkyne or azide as the third reacting component (Scheme 1). DMF was used as the solvent. The reaction gave a nearly perfect yield after 24 h at room temperature in a closed vessel. All building blocks functionalized with a carboxylic acid, which were attached to the support during the esterification reaction, underwent the CuAAC stage of the one-pot process. Thus, the efficiency of the CuAAC (Click) stage on the support was excellent. Accordingly, the yield indicated in Scheme 1 (with the exception of process h) refers to the percent of the esterification–click products on the resin, relative to the maximum possible amount, based on the initial resin loading and weight, and can also be considered as a measure of the esterification efficiency.

As mentioned above, the one-pot esterification-CuAAC with carboxylic acids has been reported twice, but in solution only.[4,14] Rolfe et al.,[14] reported a yield of about 50%, while the yield of Gao and Zheng was not reported. To our knowledge, the method reported herein is the first to functionalize polymers or any solid support and also the most efficient reaction of this type to date.

We also tried to apply the same reaction conditions to a system with an azide reagent, but without an alkyne partner (Scheme 1, reaction h). The results did not show any side reactions occurring at the azide functionality under these conditions.

One-pot esterification-Glaser and esterification-Eglinton coupling reactions

We noted that when the above esterification-CuAAC reaction conditions were run with little or no azide present, a Glaser coupling reaction tended to occur between alkynes. This is not surprising given that the Glaser coupling[10–12] is promoted by both copper(I) and bases, similarly to the CuAAC-click reaction,[10,11] and the CuAAC reaction is known to sometimes be accompanied by Glaser coupling side products.[16,19,20] However, given that a one-pot combination of esterification and Glaser coupling has not been previously reported in the literature, we decided to further examine this reaction. The Glaser coupling is much slower than the CuAAC reaction and, therefore, insignificant when an azide is present. However with no azide and with additional copper(I) iodide, the Glaser coupling can be brought to completion without a substantial reduction in the esterification yield (Table 1). Given