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A new polymer-bound *N*-hydroxysuccinimidyl active ester linker

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Abstract

Synthesis of a new *N*-hydroxysuccinimidyl resin is described and the *N*-acylation with this resin provides amide products in high yields and excellent purities. This new linker is suitable for combinatorial library synthesis. © 2000 Published by Elsevier Science Ltd.

Keywords: solid-phase synthesis; amides; acylation; and combinatorial chemistry.

Complementary to the emergence of solid phase-based combinatorial chemistry, polymer-bound reagents and linkers have become important tools in organic synthesis in recent years.[1] Unlike traditional organic reagents, polymer-bound linkers not only possess desirable reaction properties, but also tether the reaction intermediates to an insoluble polymer support. This feature allows great simplification of multiple step synthesis and makes the automation process readily feasible. Therefore, a wide range of linkers on polymer have been explored to accommodate different reaction needs.[1]

Taking into account that commercially available amines and carboxylic acids give access to a wide structural diversity in combinatorial library synthesis, we are interested in developing a versatile active ester linker on solid support to facilitate *N*-acylation reactions with simultaneous cleavage from the polymer. Several reports have described various polymer bound reagents, such as nitrophenol,[2] HOBt (1-hydroxybenzotriazole),[3] carbodiimides[4] and Kaiser oxime resin.[5] Compared to other active ester reagents, *N*-hydroxysuccinimidyl esters tend to be more stable, easy to store and give clean products in solution reactions. Recently, two groups have reported multiple-step synthesis of a linker using *N*-hydroxymaleimide and thiol.[6] Here we describe a simple method to prepare an *N*-hydroxysuccinimidyl derived linker under mild conditions using 1,2,3,4-cyclopentanetetracarboxylic dianhydride (**1**).

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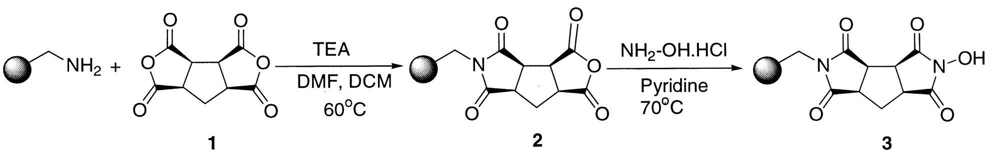
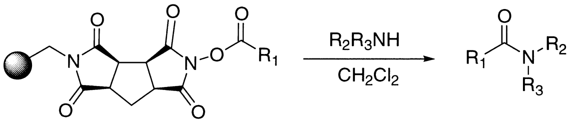
We chose dianhydride (**1**) as the starting material because it is commercially available, inexpensive and has a symmetrical structure. Dianhydride (**1**) was first dissolved in DMF, and then suspended with the aminomethyl polystyrene resin in the mixture of triethylamine, methylene chloride and DMF for 12 h at room temperature as shown on Scheme 1. After standard washing cycles, the monoanhydride (**2**) on polymer was treated with hydroxylamine in pyridine at 70°C for 5 h to provide the desired *N*-hydroxysuccinimidyl active ester resin (**3**).

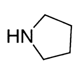
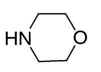
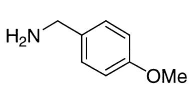
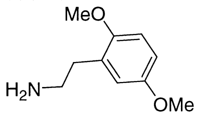
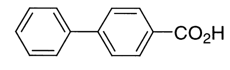
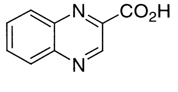
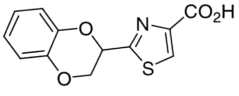
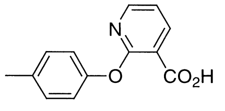


Scheme 1. Synthesis of *N*-hydroxysuccinimidyl active ester linker (**2**)

With the resin (**3**) in hand, a series of active esters were prepared using carboxylic acids and coupling reagents such as EDC or DIC. As expected, the active esters formed on this resin possessed excellent reactivity, and *N*-acylation reactions occurred instantly once the active ester resin was exposed to the amines as shown on Table 1. The reactions went to completion within 20 min. High yields and purities of products were ensured by maintaining an excess of active esters over amines in all reactions. More interestingly, the active esters formed on this resin are quite stable

Table 1
N-Acylation reactions using *N*-hydroxysuccinimidyl active ester resin



Amines (R$_2$R$_3$NH) / Carboxylic Acids (R$_1$-COOH)				
	99%* (81%**)	100% (73%)	97% (73%)	99% (68%)
	100% (78%)	100% (81%)	86% (84%)	98% (74%)
	100% (93%)	100% (90%)	97% (79%)	98% (92%)
	99% (72%)	100% (77%)	99% (86%)	100% (77%)

*Purity was determined by LC/MS-ELSD.

**Yield was isolated yield based on the amount of amine used in the reaction .

and can still give clean acylation products with high yields after storage at room temperature over 6 months.

In conclusion, a new *N*-hydroxysuccinimidyl active ester linker was prepared in two steps from commercially available aminomethyl polystyrene resin and inexpensive reagents under mild conditions. The short synthesis of the resin and the efficient *N*-acylation described here provide the advantages for the rapid and clean synthesis of a combinatorial library.

1. General procedures

1.1. N-*Hydroxysuccinimidyl resin* ***3***

Dianhydride (**1**) (25.2 g, 120 mmol) was dissolved in dried DMF (300 mL), and then added to a mixture of aminomethyl polystyrene resin (30 g, 1.72 mmol/g), triethylamine (50 mL) and methylene chloride (200 mL). The mixture was shaken with a mechanic shaker at 60°C for 12 h, then washed with DMF (3 times) and methylene chloride (3 times). After the resin (**2**) was suspended in pyridine (400 mL), hydroxylamine hydrochloride (35.8 g, 516 mmol) was added as a solid. The mixture was stirred at 70°C for 5 h. The resin was washed with DMF (3 times), water (2 times) 2-propanol (2 times), methylene chloride (3 times), then dried in vacuo for 48 h to give 40.7 g dried resin. The loading level of the resin (**3**) was 1.27 mmol/g based on the weight change after the treatment of the resin. FT-IR analysis on resin beads gave distinctive imide carbonyl absorption at 1700 cm^{-1} and typical *N*-hydroxyl group absorption at 3460 cm^{-1}.

1.2. Synthesis example using N-*hydroxysuccinimidyl active ester*

4-Biphenylcarboxylic acid (1.13 g, 5.72 mmol) was suspended with resin (**3**) (1.50 g), diisoprpylcarbodiimide (0.72 g, 5.72 mmol), triethylamine (2 mL) in methylene chloride (15 mL). The mixture was stirred for 4 h. Then the resin was washed with DMF (3 times), water (2 times), 2-propanol (2 times), and methylene chloride (3 times), then dried in vacuo for 48 h to give 1.70 g dried resin. The loading level of the active ester was determined as 0.65 mmol based on the weight change of the resin.

1.3. An example of N-*acylation from the active ester on* N-*hydroxysuccinimidyl resin*

4-Methoxybenzylamine (8.1 mg, 0.06 mmol) was added to a suspension of active ester resin (200 mg, 0.13 mmol) in 1.5 mL of methylene chloride. The reaction was complete in 20 min. The resin was washed with methylene chloride (2×2 mL) and the combined solutions were evaporated in vacuo and solid samples were formed in most cases. The products were characterized by ^{1}H NMR and LC/MS.

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