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MERRIFIELD MICROTUBE™ REACTORS FOR SOLID PHASE SYNTHESIS[1]

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Abstract: Polystyrene grafted polypropylene MicroTube™ reactors (length x OD, 25 x 5 mm) have been functionalized with chloromethyl groups (Merrifield-type) using chloromethyl methyl ether and Lewis acid catalysts. A potentiometric method using a chloride ion selective electrode has been developed to measure the loading of the Merrifield MicroTube™ reactors. A typical loading of 25-35 μmol/tube for Merrifield MicroTube™ reactors has been achieved. Several reactions performed on Merrifield MicroTube™ reactors demonstrated that they are excellent supports for solid phase synthesis. As a result of the ease with which radiofrequency memory tags can be associated with and separated from the supports, these MicroTube™ reactors can facilitate the synthesis of combinatorial libraries.

Combinatorial chemistry is becoming an increasingly powerful tool in lead identification and lead optimization for drug discovery, especially in the design and synthesis of libraries of small organic compounds.[2-5] To facilitate combinatorial synthesis utilizing the 'directed sorting' strategy,[6] we and others invented SMART[7-8] (Single or Multiple Addressable Radiofrequency Tag) microreactors. One kind of these SMART Microreactors, called MicroTube™ reactors which are polystyrene-grafted polypropylene tubes each containing an RF tag, has been functionalized with chloromethyl groups (Merrifield-type). The advantages of using the MicroTube™ reactors are: 1) the ability to hold RF tags for use in Radiofrequency Encoded Combinatorial (REC) chemistry; 2) no resin loading required; 3) the ease to wash away excess reagents used in the library synthesis; and most importantly 4), the capability of producing discrete compounds in multimilligram quantity per MicroTube™ reactor.

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In this paper, we wish to report: (1) a result of the chloromethylation reaction for MicroTube™ reactors based on Feinberg/Merrifield[9] procedure; (2) an accurate and convenient method for determination of the loading of Merrifield MicroTube™ reactors;[10] and (3) demonstration of high quality of Merrifield MicroTube™ reactors as a novel support for solid phase synthesis.

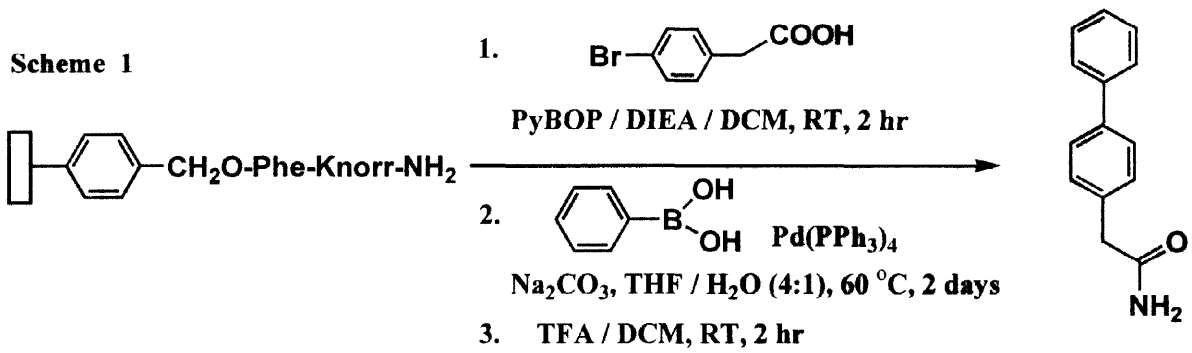
Merrifield resins are normally prepared at elevated temperature by Friedel-Crafts chloromethylation of a styrene-divinylbenzene copolymer using chloromethyl methyl ether and Lewis acid catalysts including $ZnCl_2$,[9] $BF_3 \cdot Et_2O$[11] and $SnCl_4$.[12] After extensive optimization of reaction conditions, we have developed a chloromethylating method suitable for polystyrene grafted polypropylene MicroTube™ reactors with the following features: (1) a desired loading (25-35 μmol/tube) of chloromethylation on MicroTube™ reactors has been achieved at room temperature for the first time; (2) only a minimal amount of chloromethyl methyl ether is used; (3) it is not only less expensive, but also safer since the reactions are carried out at room temperature with a minimal amount of chloromethyl methyl ether.

Conventionally, the loading of Merrifield resins is determined by elemental analysis of incorporated chlorine or titration of pyridinium chloride formed after hot pyridine treatment of Merrifield resins.[12] Since most of the mass of the MicroTube™ reactors is polypropylene and the percentage of incorporated chlorine in Merrifield MicroTube™ reactors is extremely small, elemental analysis would not be accurate. Titration is more tedious and requires more Merrifield MicroTube™ reactors for analysis. We have now developed a potentiometric method[10] that permits a measurement of chloromethylation using chloride ion selective electrode (ISE). This method is simple, convenient and very accurate. It gives accurate analytical results in a linear range from 5 to 150 μmol chloride per Merrifield MicroTube™ reactor.

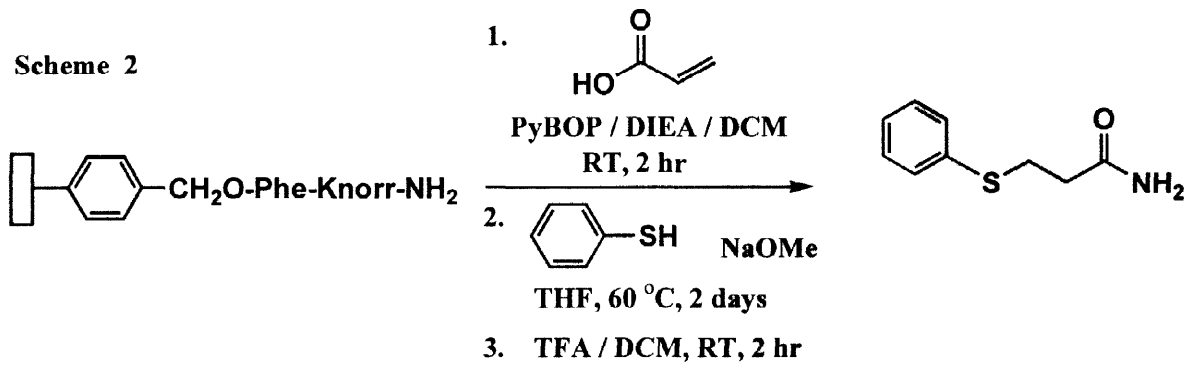
Several reactions were performed to test the performance of Merrifield MicroTube™ reactors in organic synthesis. Merrifield MicroTube™ reactors (28 μmol/tube) were first reacted with Boc-Phe-OH using the method by Gisin to form the solid phase-bound ester.[13] After the Boc group was removed with 25% TFA in DCM, Knorr linker (2.9 eq.) was coupled to the MicroTube™ reactors using PyBOP (3.0 eq.) and DIEA (6.0 eq.) in DCM (1 mL/tube) at room temperature for 2 hr. A complete reaction was demonstrated by a negative Kaiser test. The loading (22 μmol/tube, 79% overall after four steps) of the MicroTube™ reactors was determined by Fmoc de-protection. As shown in Scheme 1, 4-bromophenylacetic acid was coupled to the resulting free amine under coupling conditions described above. Suzuki coupling with phenylboronic acid was performed according to the methods on resins

reported by Backes and Ellman.[14] Quantitative yield of the desired product was obtained after cleavage using TFA / DCM (1:1, 3 mL total) at room temperature for 2 hr. HPLC showed > 95% purity with 79% overall yields from Merrifield MicroTube™ reactors. Both ^{1}H NMR and MS showed that the product has the desired structure. Under the same conditions, acrylic acid was coupled to MicroTube™ reactors as shown in Scheme 2, followed by Michael

Scheme 1



Scheme 2



addition of thiophenol using the methods for resins by Chen et al.[15] The desired product was obtained in a 75% overall yield after cleavage under the same conditions as Scheme 1. HPLC showed that the product is over 95% pure. Other successful examples include the synthesis of anticancer agent Epothilones using Merrifield MicroTube™ reactors reported recently by K. C. Nicolaou.[16]

In summary, we have developed a chloromethylation method suitable for polystyrene grafted polypropylene MicroTube™ reactors. A simple, accurate and convenient potentiometric method has

also been developed for the loading determination of Merrifield MicroTube™ reactors. The method is also suitable for the loading determination of Merrifield resins. Several reactions performed on Merrifield MicroTube™ reactors demonstrated that they are excellent support for solid phase synthesis. A variety of acid-labile linkers derived from the Merrifield MicroTube™ reactors have been developed and will be reported in due course.

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10. Detailed ISE method: Merrifield MicroTube™ reactors (5) were treated individually with dry pyridine (3 ml each) at 100 °C for 2 h. The pyridine is removed under reduced pressure. De-ionized water (9.8 ml) and Ionic Strength Adjuster (ISA, 0.2 mL, AIT ORION 940011) were added, and the resulting mixture was stirred at room temperature vigorously for 2 min. The chloride concentration is then measured potentiometrically using a chloride-selective electrode (ATI ORION 9417BN) and the loading of the Merrifield MicroTube™ reactors is calculated using the following formula: loading (μmol) = 10000 x $10^{(V-a)/b}$ (V is the measured potential of the sample, and constants a and b are calculated by standard [Cl^-] sample measurements). Typical Merrifield MicroTube™ reactors have a loading of 30 μmol ± 10% RSD (Relative Standard Deviation).
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