Report

A Simple, Inexpensive Reactor with Condenser for Use in Combinatorial Chemistry

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Reports

A Simple, Inexpensive Reactor with Condenser for Use in Combinatorial Chemistry

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Introduction. The advent of combinatorial chemistry has led to an explosion of novel methods to prepare large libraries of compounds.[1−3] While there have been numerous reviews and books published on the synthetic methodology needed to prepare diverse chemical structures, relatively little has been published on the equipment necessary to conduct combinatorial chemistry.[4] Examination of the literature on combinatorial chemistry indicates that there are numerous manufactures that supply reaction vessels suitable for the synthesis of chemical libraries.[5] These systems vary greatly in price and functionality; however, almost all of them utilize some type of reaction vessel, a method to mix reagents, and a method of heating or cooling these vessels. Refluxing in these reaction vessels is typically done using airflow around the headspace of the reaction vessel, although a few companies have instruments that have cooled condensers that can be added to the system.[5]

Recently, we were interested in synthesizing a series of bicyclooctanes as potential inhibitors of a critical protein−protein interaction involved in herpes simplex virus.[6,7] Preliminary analysis indicated that the synthesis of these compounds required refluxing for the reaction to occur.[6,7] Examination of the literature failed to provide a simple, inexpensive method to reflux a large number of reactions simultaneously. After exploring a variety of prototypes, we have devised a reaction vessel that includes a built-in condenser. The condenser can be prepared using readily available materials found in any standard synthetic laboratory for around $1.00 per reaction vessel. To utilize this system with multiple reactions, we also devised a simple water manifold that can dispense chilled water to multiple condensers simultaneously. Testing of our system indicated that the condenser provided efficient condensation for a variety of standard organic solvents. In addition, we also demonstrate the utility of combining multiple reactors to simultaneously conduct 21 Diels−Alder reactions.[8] In this report, we detail the preparation and testing of our system.

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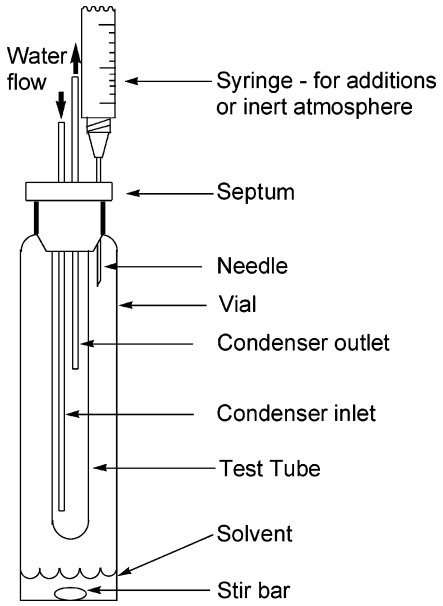

Figure 1. Schematic of the reaction vessel including condenser. Each part is listed along with its location. A description of each part is listed in Table 1.

Table 1. Parts and Suppliers Necessary to Construct the Reaction Vessel Outlined in Figure 1

part	part number and supplier
vial (25 × 95 mm, 8 dr)	03-339-21H (Fisher Scientific)
septum (19/22)	Z10,076-5 (Aldrich Chemical Co.)
test tube (10 × 75 mm)	14-958B (Fisher Scientific)
capillary tube (1.1−1.2-mm i.d., 75-mm length)	08-261-2A (Fisher Scientific)
microbore tubing (1.27-mm i.d.)	14-170-15E (Fisher Scientific)

Results and Discussion. Figure 1 and Table 1 outline the construction of the reactor and the corresponding parts necessary for its construction. The reaction vessel consists of a standard glass vial with a total volume of 30 mL. The dimensions of the vial (25 × 95 mm) allows for a large headspace in which to place the condenser. The condenser is constructed of a standard glass test tube (10 × 75 mm) placed into the bottom of a rubber or silicone septum (19/22, bottom part 9.2 mm i.d., 15.9 mm o.d.). The test tube fits snugly into the septum and requires no additional method of support. During our use of this system, we have never experienced any problems with the test tube dislodging from the septum, even when filled with water. Silicone sealant may be used to secure the tube if necessary.

To supply water to the test tube, two glass tubes (1.1−1.2-mm i.d.) were added. We utilized small-gauge tubing sold as capillary tubes for the water inlet and outlet. To get the glass tubes through the septa, two holes were created in

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the top of the septa using a large bore needle. The glass tubes were placed into the holes and orientated such that the exit tube was positioned higher than the inlet tube to allow the test tube to fill with water.

The entire condenser system can be added to the vial after the addition of reagents and solvents. Since the majority of the system consists of glass, the entire condenser unit can be heated in the oven to dry the system for use in water-sensitive reactions. If high temperatures are needed, silicone septa should be utilized for the construction of the condenser (in general rubber septa can be used to a temperature of around 85 °C while silicone septa can be used to a temperature of 200 °C). If additional reagents need to be added during the reaction, we have found that there is enough room between the test tube and the walls of the reaction vial to allow for a 25-gauge needle to pierce the septum and add reagents. The use of a needle also allows for the presence of an inert atmosphere to be maintained and to prevent the build-up of pressure in the vessel.

To connect the condensers to a water source, we utilized microbore tubing (1.27 mm i.d.). This tubing fits snugly over the capillary tubes and requires no additional means to secure the tubing. The microbore tubing can be connected to a water inlet using a small pipet as an adapter unit between the microbore tubing and larger bore tubing typically used to connect condensers to a water source. Flow rates are typically lower as a result of the small diameter of the tubing used in our system.

To connect multiple condensers, two approaches were investigated. In the first approach, each condenser was connected in a series in which the outlet of one was connected to the inlet of the other. We found that this method did not provide the best means of cooling reactions that were toward the end of the series. Thus, we investigated a second method. In the second method, all condensers were connected together in parallel from a common water source. This required a water manifold to distribute water to all condensers simultaneously. Our water manifold is described in Figure 2.

The water manifold simply consists of a standard filter flask with a rubber stopper containing a hole. Multiple microbore tubing lines are passed through the hole, and the residual space left in the hole is sealed with silicone sealant. Typically, we found that a standard 6-mm hole could accommodate five lines. Correspondingly larger holes would be able to accommodate more lines. The addition of water into the sidearm of the filter flask results in the partial filling of the flask with water, and the resulting buildup in pressure dispenses water to each of the condensers. The water manifold described here has an additional advantage in that the flask can be placed into an ice bath. This helps to chill the water present in the filter flask and helps in the condensation of low boiling solvents. The outlet lines from each condenser were taped together and placed into a piece of tubing, which discharged into a sink.

To test our design, we simultaneously heated five reactors containing five common organic solvents. Each reactor was charged with 3.0 mL of solvent, and the reaction was refluxed for 5 h. At the end of this time, the amount of solvent left in the reaction vessel was measured. The results, outlined in Table 2 indicate that the condenser provided efficient condensation of the solvents tested.

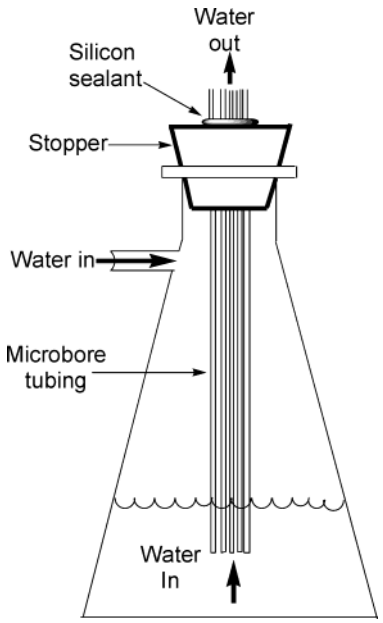

Figure 2. Schematic of the water manifold used in these studies.

Table 2. Solvents Tested Using the Reaction Vessel outlined in Figure 1

solvent	bp (°C)	amt recovered (mL)[a]
THF	65−67	2.6, 2.6, 2.6, 2.6, 2.6
toluene	110	2.8, 2.8, 2.8, 2.8, 2.8
CH_2Cl_2	40	2.5, 2.7, 2.5, 2.6, 2.5
DMF	153	2.9, 2.9, 2.9, 2.9, 2.9
DMSO	189	2.8, 2.9, 2.9, 2.9, 3.0

[a] Five separate reaction vessels were utilized, each containing 3.0 mL of solvent. Each value represents the volume of solvent recovered after 5 h of refluxing. Standard error of measurement is 50 μL.

We next chose to examine the system by scaling up to run 21 simultaneous Diels−Alder reactions.[8] Each one of the 21 reactors was charged with *N*-methyl-maleimide and cyclopentadiene, and the reaction was conducted for 3 h in refluxing toluene.[8] To run 21 reactions, we found that two water manifolds were needed. One of the water manifolds was scaled to hold 18 water lines, while the other contained the standard 5 lines. Attempts to create a larger manifold failed as a result of excessive back-pressure, thus highlighting a limitation of the current design.

Each of the 21 reactors was examined for the presence of the desired product using both TLC and HPLC.[8] Both analyses indicated the presence of the desired product in high yield for all 21 reactors. During this study, we also observed that if a reactor was not cooled properly, the reaction was incomplete and produced numerous side products, as judged by TLC analysis. Thus, care needs to be taken to ensure that all condensers have the proper flow of water.

Summary. We have outlined the construction of a simple, inexpensive reaction vessel that contains a built-in condenser. The vessel can be constructed from easily available materials found in the common organic laboratory and each reaction vessel can be prepared for around $1.00. This inexpensive

system should thus find utility in combinatorial chemistry for the synthesis of libraries of compounds.

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Supporting Information Available. Experimental details and the HPLC traces for all 21 reactions along with traces for toluene, *N*-methylmaleimide and cyclopentadiene are included as Supporting Information. The material is available free of charge via the Internet at http://pubs.acs.org.

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