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Rapid Chemical Reaction Workup Based on a Rigid Solvent Extraction

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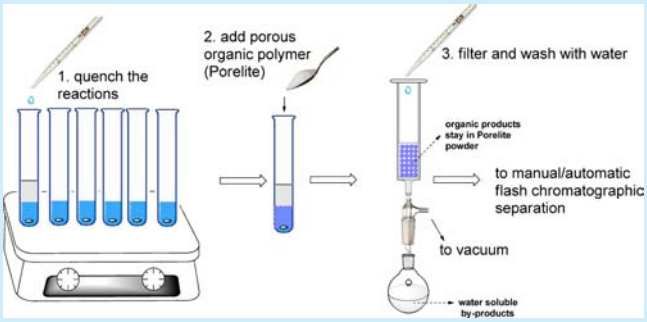
Supporting Information

ABSTRACT: The conventional chemical reaction workup based on liquid–liquid extraction is a time- and labor-consuming practice. We have developed a substantially faster technique for the routine workup that relies on a porous organic polymer (Porelite) supported solvent phase to extract organic products from an aqueous reaction mixture. We call this process rigid solvent extraction. Using this technique, the tedious liquid–liquid extraction can be replaced by a simple filtration, making parallel operation and automation feasible.



During the discovery stage of pharmaceuticals, agrochemicals, materials, and many other related research endeavors, a large number of organic compounds need to be synthesized for testing their biological activities or other properties, in amounts that range from milligrams to grams. The bottleneck in the synthesis of large number of compounds has, in truth, always been the isolation and purification of products, rather than the reactions themselves.[1] This is especially true nowadays when the setup of reactions can be done efficiently using state of the art parallel synthesis equipment. Column chromatography is often the preferred method to purify small amounts of organic mixtures. Since the introduction of flash chromatography by Still and co-workers in 1978,[2] and especially after the emergence of commercial automatic flash chromatography systems, the efficiency of chromatography purification has also been greatly improved. However, there is still a technology gap between reaction setup and flash column purification. After completion of reactions, the reaction mixture usually cannot be directly injected into a manual or automated flash chromatography system. Typically, a workup or cleanup procedure is needed to remove active intermediates, catalyst(s), water-soluble inorganic byproducts, and/or polar solvents, all of which can affect the chromatographic separation. Thus, the workup/cleanup process is still labor intensive and time-consuming.

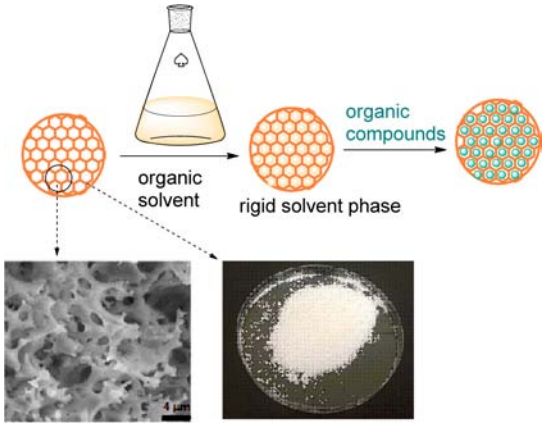


Figure 1. Concept of rigid solvent extraction (RSE).

The most common reaction cleanup procedure continues to be a liquid–liquid extraction (LLE) using a separatory funnel. In a typical procedure, after the reaction is complete, the reaction mixture is quenched with a suitable aqueous solution to destroy excess amounts of reagent/intermediate/catalyst and to dissolve water-soluble byproducts. Then, the aqueous mixture is extracted with organic solvents in iterative fashion, and the combined organic layers are washed with an aqueous solution to remove inorganic byproducts. Next, the organic phase is dried using a drying agent and filtered, and the solvents are removed under vacuum. Finally, the residue is dissolved in a minimum amount of relatively nonpolar solvent (wet loading) or mixed with silica gel (dry loading) and loaded onto a flash chromatographic column for further purification.

Liquid–liquid extraction (LLE) is indeed labor- and time-consuming, especially when large numbers of samples are involved. Additional disadvantages of LLE include the use of relatively large volumes of solvent, possible emulsion formation blurring the separation between liquid phases, and a relatively high chance of contact with potentially hazardous chemicals.

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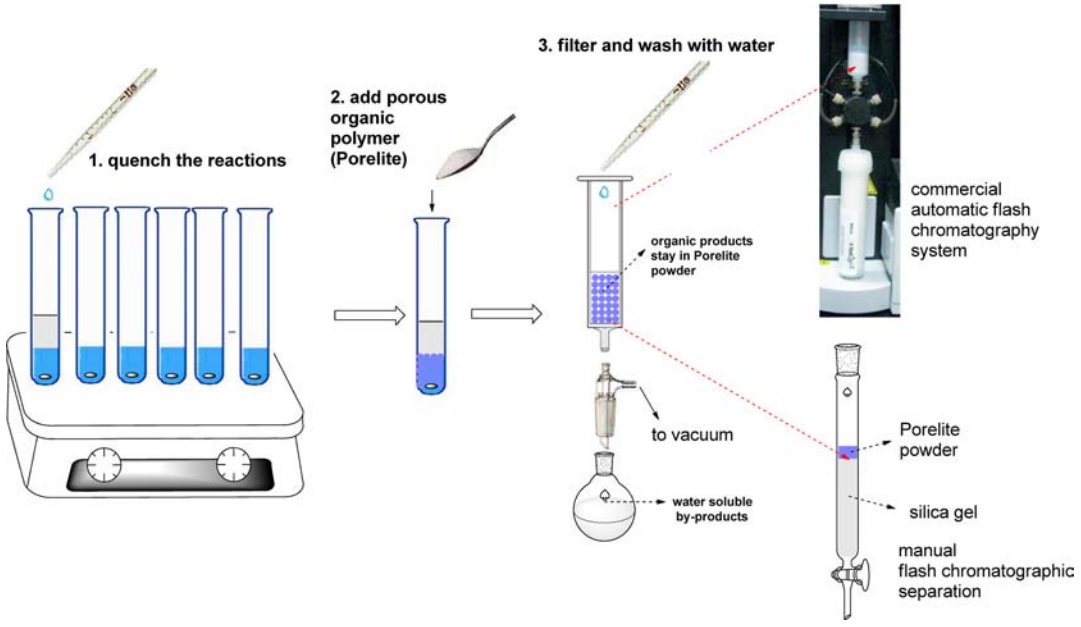

Figure 2. Procedure for rigid solvent workup.

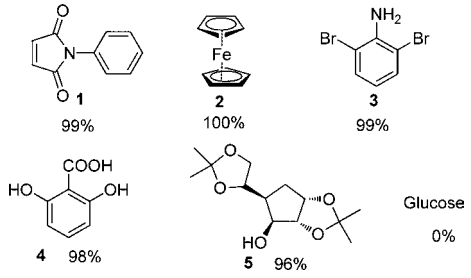

Figure 3. Recovery rate of test compounds. Procedure: the test compound was dissolved in 2 mL of ethyl acetate, and 4 mL of 20% NaCl solution was added with stirring (this is a simulation of the reaction mixture after quench), then 2 mL of polymer was added. After stirring for 2 min, the mixture was filtered and washed with water (ca. 4 mL) and finally washed with acetone to recover the product.

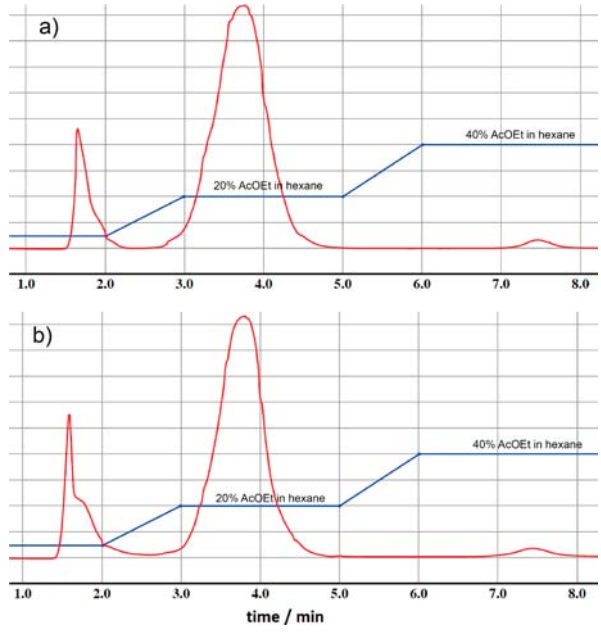

Figure 4. Chromatographic trace for separation of a test compound mixture (a, traditional loading; b, dry loading using Porelite) (the test compound mixture contains 1:1:2 mixture of compound **1**, **2**, and *p*-Cl-benzaldehyde).

These problems have led scientists to develop various alternatives, but none has provided a universal solution.[1]

We now report a substantially faster technique for the routine workup of chemical reactions, which we call rigid solvent workup. The idea is simple. The reaction is conducted in the usual way and quenched with a suitable aqueous solution. Instead of using a conventional liquid organic solvent to extract the aqueous reaction mixture, we use the affinity of a porous honeycomb-like organic polymer to a liquid organic solvent to embed the latter in the polymer support. In this way, the entrenched solvent carries the extraction (Figure 1). Our rigid solvent workup is general (i.e., works for most reactions), fast, uses minimal amount of solvents, reduces the chance of contact with hazardous chemicals and is capable of parallelization and automation.

In our rigid solvent extraction, the *combination* of a solid porous organic polymer and a liquid solvent forms a new type of phase, a rigid solvent phase (Figure 1), which is rigid compared to the usual liquid solvents. The rigid solvent phase can be easily and quickly separated from the aqueous phase by simple filtration, and the desired products can be eluted by a suitable organic solvent during chromatography. In this way, the tedious and time-consuming LLE is avoided, and a common problem in LLE—emulsion formation is eliminated because the separation of two liquid phases is not necessary. Because only stirring and filtration are involved, automation and parallel setups are feasible.

Commercially available microporous and macroporous polymers (e.g., XAD series resin from Dow Chemicals) are not ideal porous supports because they have relatively small pore volume (normally 1—1.8 mL/g), and they usually swell or shrink in different solvents, causing problems in chromatographic separations. We selected a new type of porous polymer, a high internal phase emulsion polymer (polyHIPE) containing extremely large cavities interconnected by a series of smaller

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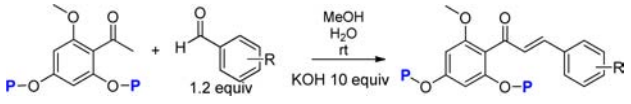
Table 1. Synthesis of a Chalcone Library Using Traditional and New Workup Protocols



P	aldehyde (R)	yield % (traditional)	yield % (new method)
allyl	4-methoxy	73	82
allyl	2,4-dimethoxy	90	92
allyl	3,4,5-trimethoxy	97	97
allyl	4-pyridinyl	55	65
allyl	2-pyridinyl	84	84
allyl	2-furanyl	87	87
MOM	4-methoxy	91	92
MOM	3,4-methylenedioxy	61	62
MOM	3,4,5-trimethoxy	78	76

pores (Figure 1).[3] We synthesized this polyaromatic polymer using a modified version of literature methods.[3] This material (Porelite) has large pore volumes (>90%, see Figure 1) enabling greater holding capacity for organic liquids and lower resistance to the flow of liquids.

The procedure for rigid solvent workup is straightforward (Figure 2). Step 1: The reaction is conducted in the usual way and quenched with a suitable aqueous solution. Step 2: After the porous polymer (Porelite, ca. 3 mL for every 1 g of product) is added to the reaction mixture, vacuum or nitrogen/air purging removes excess amount of organic solvent (aqueous phase is still in reaction mixture). Step 3: The reaction mixture entrenched in the polymer is filtered and washed with water (or HCl or Na_2CO_3 solutions to remove basic or acidic byproducts). For automatic flash chromatographic separation, the polymer is filtered using an empty loading cartridge, which can be directly attached to a commercial system. For manual chromatographic separation, a regular Buchner filter is used; the polymer powder is then loaded directly onto a manual flash silica gel column (dry loading, to the top of silica gel). The total process is no longer than 5−10 min.

The scope of our rigid solvent extraction is potentially superior to traditional LLE because there are no losses due to iterative solvent extraction. As proof of concept, target compounds (Figure 3) were dissolved in organic solvents. and a solution of NaCl was added during stirring (to simulate the quenching of a chemical reaction). Our rigid solvent extraction technique (using the protocol shown in Figure 2) gave an excellent recovery for most test compounds screened (including hydrocarbons, phenols, heterocycles, acids, and bases; see Figure 3). The only exception was the extraction of glucose, but this result is not surprising because glucose is soluble in water and not soluble in organic solvents.

Our new rigid solvent workup can serve as a convenient input for flash chromatograph separations (Figure 2). The quality of the separation achieved with our new workup method (e.g., similar peak width) is similar to a conventional loading method (Figure 4).

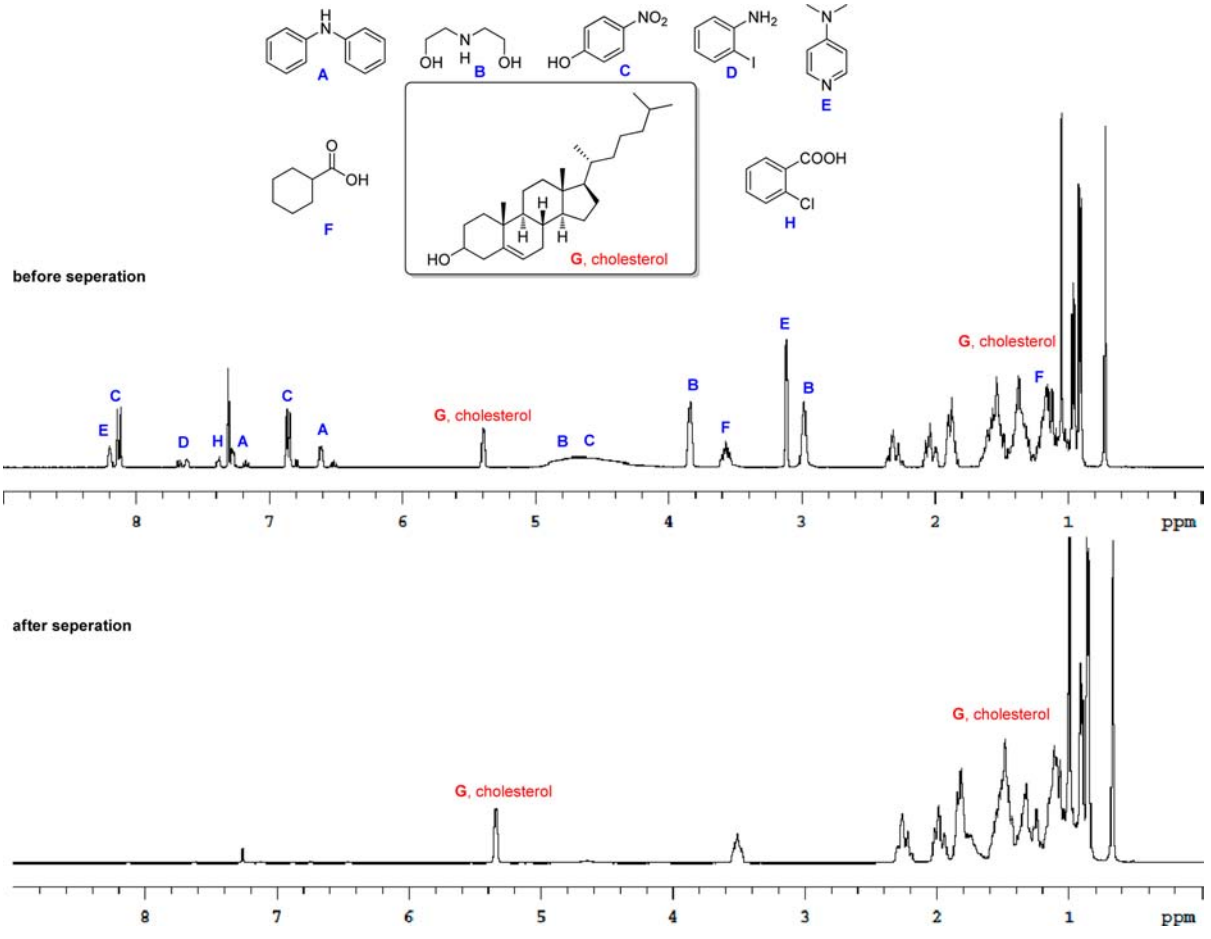


Figure 5. Use of rigid solvent workup to remove acidic and basic impurities.

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A rigid solvent workup also worked very well in a real synthesis project (Table 1), namely, building a chalcone library for biological evaluation against Leishmaniasis.[4] Our workup protocol, using Porelite, only needed a simple filtration for each sample and could be set up in parallel using a commercially available filtration station (see Supporting Information). Because of its simpler operation, human contact with potential toxic materials was minimized.

The purification ability of Porelite was further demonstrated by its capacity to remove acidic and basic impurities. To showcase this ability, we used a rigid solvent workup to separate a target compound (e.g., cholesterol) from a mixture of various organic acids and bases (Figure 5). A mixture of cholesterol and various acids and bases (Figure 5, top structures) were first dissolved in ether, and water was added next. Then Porelite was introduced, the mixture was filtered, and the polymer bed was washed with HCl solution (1 M), NaOH solution (1 M), and then water again. Finally, the polymer pad was washed with ether. Cholesterol was recovered in 99% in good purity (Figure 5, bottom)

In summary, we have developed a substantially faster, yet efficient, technique for the routine workup of chemical reactions, which we call rigid solvent extraction. We have replaced the traditional liquid−liquid extraction with a simple filtration using Porelite, a highly porous polymer. We have identified a commercialization partner, so we expect Porelite to be available in the future. Other applications of this new technique are currently being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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