Ultrasound-promoted scavenging: a rapid parallel purification for solution phase combinatorial synthesis

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Ultrasound irradiation enhances the mass transfer and reaction rate in scavenging, avoiding the trouble of time-consuming purification procedure in solution-phase parallel synthesis. An application of this technique is demonstrated in the scavenging of excess isothiocyanates from reaction mixtures.

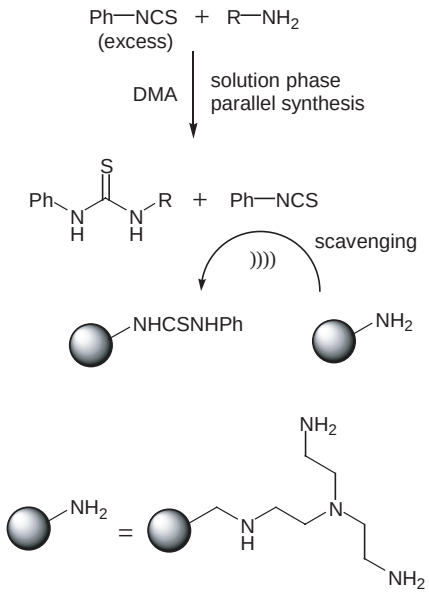
Keywords: combinatorial chemistry, purification, scavenger, sonication, isothiocyanates

Over the past few years, solution-phase high throughput synthesis has emerged as a versatile and efficient method in combinatorial chemistry for the rapid generation of chemical libraries, accelerating both lead discovery and optimisation programs.[1] Solution-phase synthesis has numerous benefits over solid-phase synthesis, such as the range of accessible reactions, use of in-process controls and flexible choice of solvents.[2] However, the rapid purification of library compounds and intermediates becomes a bottleneck by using solution chemistry. In this context, many innovative purification methods have recently been disclosed to overcome this inherent drawback often associated with solution-phase reactions.

The most widely employed method among them is the use of polymer-supported scavenger reagents, which allows the use of excess reagents to drive reactions to completion, followed by facile removal of excess reagent from the final production.[3,4] Unfortunately, the technique of using solid-supported scavenger reagents has drawbacks such as the longer reaction times. With gel-type beads, the majority of reactive sites are positioned inside the particles. Hence, hindered access to functional groups within the resin core, and the biphasic nature of the reaction systems that contain polymer-bound entities result in sluggish reactions. Because of these limitations, the availability of rapid and efficient scavenging methods for the solution-phase parallel synthesis is highly desirable. Despite the importance of scavenging efficiency, however, few studies have been conducted in this area. In a recent publication, Dallinger and co-workers have described a microwave-assisted scavenging technique.[5]

The application of ultrasonic irradiation in a wide variety of chemical transformations has gained significant potential in the last two decades. In the same way, ultrasound irradiation has also been found to be useful in the solid phase synthesis of peptides[6] and non-peptidic small organic molecules.[7] The introduction of ultrasonic waves to the solid phase synthesis, which remarkably promotes the diffusion of reagents into the resin matrix, results in enhancement of the reaction on the resin. Moreover, ultrasound has also been demonstrated to be useful in resin washing after solid-phase synthesis.[8]

It may be anticipated that scavenging performed in heterogeneous systems may have advantages through sonication. As, no attention has been paid to this potentially useful method, we decided to develop a novel ultrasound-promoted scavenging method by which some drawbacks of heterogeneous scavenging reactions related to the use of polymer supports could be overcome. Thioureas are important pharmacophores in many biologically active compounds. Thus, the preparation of disubstituted thioureas from phenyl isothiocyanate and amines was selected as a model reaction to test the practicability of our method (Scheme 1).



Scheme 1

As a model study, the reaction of phenyl isothiocyanate and 4-chloroaniline was employed. After the reactions, the excess isothiocyanate was scavenged on the resin by forming the corresponding thiourea using a polyamine scavenger. In the case of the dendritic scavengers, the number of equivalents was calculated on a molar basis. Hence, less resin was required to achieve similar scavenging efficiency. An excess of phenyl isothiocyanate (1.5 equiv) was added to a solution of 4-chloroaniline in DMA and the mixture was irradiated with ultrasounds. The use of excess phenyl isothiocyanate was needed to ensure the complete conversion of the amine to the corresponding thiourea. When total consumption of the amine was observed (using HPLC), the resulting solution was treated with polyamine scavenger under both sonication and 'silent' conditions at ambient temperature. The reaction mixtures were sampled and the conversion of isothiocyanate was determined by HPLC.

As shown in Fig. 1, when ultrasound irradiation was employed, the complete conversion of excess isothiocyanate could be observed within 60 min. Only a trace amount of excess reagent remained according to HPLC analysis (Fig. 2). In contrast, only 61% of excess isothiocyanate was scavenged after 120 min in the blank experiment ('silent').

These examples demonstrate the beneficial effect of sonication.

To generalise the presented method, a model library of N, N'-disubstituted thiourea was prepared and purified in parallel manner employing the ultrasound-promoted procedure described above. The scavenging process was carried out in an apparatus illustrated in Fig. 3. The purity of the library (in the

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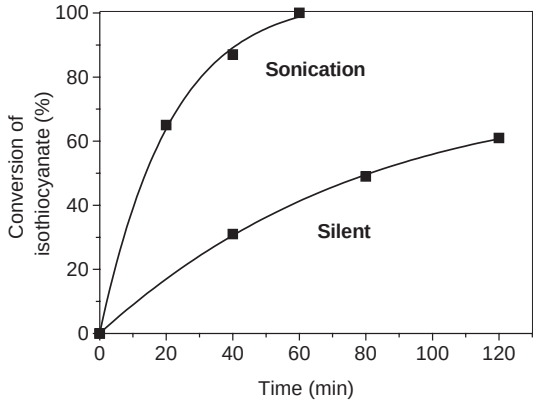

Fig. 1 Conversion of phenyl isothiocyanate as a function of time: comparison between sonicated and 'silent' scavenging.

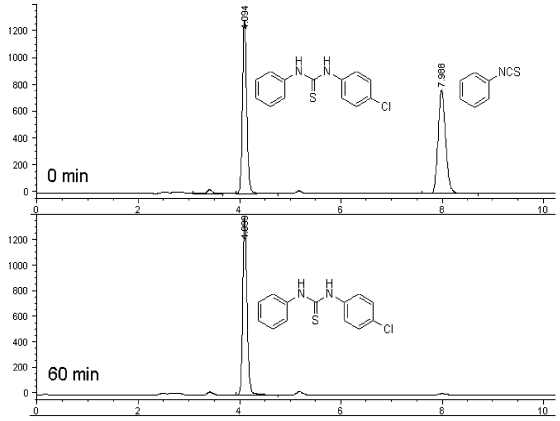

Fig. 2 HPLC monitoring of scavenging process under ultrasound irradiation.

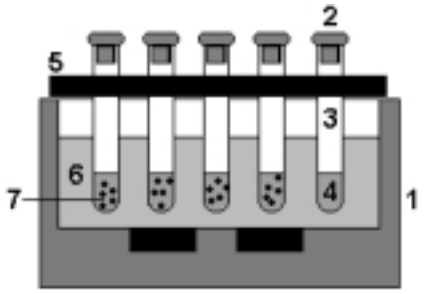

Fig. 3 Apparatus for ultrasound-promoted parallel purification. 1, ultrasonic clean bath; 2, rubber plug; 3, test tube; 4, reaction mixture; 5, foamed polystyrene plate; 6, water; 7, scavenger resins.

range of 96–99%) was confirmed by HPLC and the results are shown in Table 1.

Presumedly, the scavenging process works in two ways: (a) sonication accelerates a range of organic reactions, logically, including reactions between excess reagents with the reactive moieties on the network of polymer scavengers; (b) ultrasound intensifies the mass transfer in heterogeneous systems. In scavenging procedures, the scavenged chemicals must overcome the resistance of mass transfer and steric hindrance caused by gel networks to access the reaction sites of the scavenger resins. The creation of pressure differentials around the imploding cavitation bubble can create high-speed solvent jets that accelerate the movement of solute particles to the gel network of the resin support, resulting in enhancement of the reaction. Hence, the increase in the speed of the mass transfer may be an important fact in this course.

Table 1 Scavenging efficiencies of isocyanates in model reactions

Entry	R	Yield[a]/%	Purity/%, HPLC
1	*i*-propyl	79	97
2	*n*-butyl	80	99
3	cyclohexyl	82	99
4	benzyl	86	98
5	Ph	84	96
6	4-Me-Ph	81	97
7	4-Cl-Ph	90	99
8	1-naphthyl	89	98

[a]Isolated yields.

In summary, we have developed a rapid protocol for the parallel purification of solution phase libraries using sonication technique, taking advantage of ultrasound-promoted mass transfer and reaction processes.

Experimental

All reagents were available commercially. The polyamine scavenger resin employed in our experiments, tris (2-aminoethyl) amine resin, was purchased from Advanced ChemTech Ltd. (0.8 mmol/g, 100–200 mesh, DVB cross. 1%). Sonication was performed in SK 2200H clean bath with a frequency of 59 KHz and a nominal power 80 W made by Shanghai KUDOS Ultrasound Instrument Co., Ltd. The reaction temperature was controlled by addition or removal of water from the ultrasonic bath. Analytical HPLC analysis was performed on Hewlett-Packard 1100 instrument, using a reversed phase Zorbax Extend-C18 (5 μm) column (4.6 mm × 250 mm). Aqueous MeCN (MeCN: H_2O = 7:3 vol) was chosen as mobile phase.

General procedure: To an array of test tubes were added phenyl isothiocyanate (0.15 mmol), various amines (0.10 mmol) and N, N'-dimethylacetamide (DMA, 3 ml). The mixture was irradiated at room temperature for 15 min in an apparatus illustrated in Fig. 3 (sonication was continued until amines had disappeared as indicated by HPLC). The scavenger resin (0.5 g, 8 times molar excess of amino groups) was then added to each test tube and the mixtures were sonicated for further 1.5 h. After completion of the scavenging, the resulting suspension was filtered. The solvents were removed *in vacuo* and the residues were washed with water (0.5 ml), collected by suction, and then dried. The purity of the library was determined by HPLC.

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