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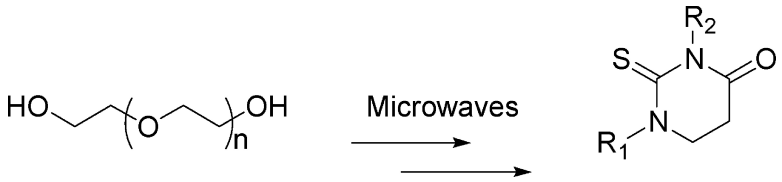

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Soluble Polymer-Supported Synthesis of Thioxotetrapyrimidinone by Focused Microwave Irradiation

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With more and more therapeutic targets emerging from chemical genomics research, combinatorial chemistry provides fast access to large quantities of structurally diverse libraries to fuel the chemical genetics. Limitations in efficiency of classical chemical synthesis resulting from tedious workup and purification can be overcome by solid-phase synthesis due to advantages such as easy and fast purification.[1,2] However, solid-phase chemistry suffers from various problems, such as the heterogeneous nature of the reaction condition, a reduced rate of reactions, solvation of the bound species, and mass transport of reagents. We have been interested in employing liquid-phase combinatorial technology as a means of efficient constructing multifunctional libraries.[3] This strategy enables standard solution-based chemistry to be utilized, and purification of the is just like that of solid-phase reactions. Furthermore, monitoring the progress of reactions on the support is significantly simplified by using conventional analytical methods.[4]

Recently, combinatorial organic synthesis has focused on the generation of non-peptide small molecules with potential therapeutical value. Compounds with a hydantoin structural motif have been identified as displaying a wide range of biological activities (Figure 1).[5−10] For example, fosphenytoin as a sodium channel antagonist is used for the treatment of epilepsy. Sulfahydantoin has been studied with respect to inhibition of serine proteases. It has been reported that the six-membered ring of disubstituted 2-thioxotetrahydropyrimidin-4-ones, analogues of hydantoins, provides better spatial configuration to exert its hypoglycemic activity.[11]

The practicality of microwave irradiation in chemical reaction enhancement has been recognized for increasing reaction rates and formation of cleaner products.[12] It is clear that the synergistic application of microwave technology to rapidly synthesize biologically significant molecules on the polymer support[13] would be of great benefit for accelerated library generation and as a useful tool for a drug-discovery program.[14] Although a number of strategies for synthesis of hydantoin analogues libraries have been reported,[15−29] application of microwave technology to facilitate multistep thioxotetrapyrimidinone synthesis on the soluble support has not been demonstrated. We have adapted herein an integrated strategy using both a combinatorial and a microwave approach from readily available building blocks to the expeditious synthesis of 2-thioxotetrahydropyrimidin-4-one derivatives.

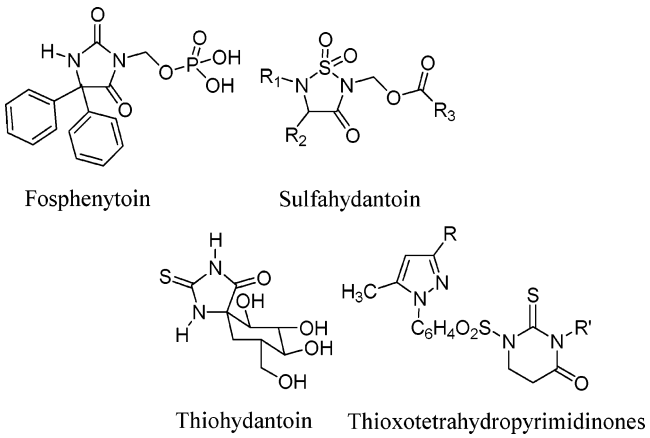

Figure 1. Examples of biologically active hydantoins and analogues.

The general synthetic route toward thioxotetrapyrimidinones is given in Scheme 1. Soluble polymer support (HO-PEG-OH, MW ∼ 6000) dissolved in methylene chloride was reacted with 3-chloropropionyl chloride in a microwave cavity for 4 min. For the comparison to the conventional thermal heating, coupling reactions were carried out in refluxing methylenechloride (preheated oil bath) for 4 min using the same stoichiometry; however, the reaction did not proceed at all. Reaction mixtures were purified through a simple precipitation and filtration to remove unreacted reagents and side products. The same workup precipitation was followed at each step of the present reaction sequence. Nucleophilic substitution of immobilized chloropropionyl ester **1** with several primary amines was carried out in 120-W microwave exposures within 15 min to give compound **2**. By the use of regular heating, the reaction was complete after 20 h of reflux. Following ether washing and drying of PEG-bound secondary amines **2**, various isocyanates (2.2 equiv) were incorporated through microwave irradiation within 10 min to give thiourea intermediates **3**. The control reaction was then performed under normal thermal heating in refluxing methylenechloride (preheated oil bath) for 10 min, using identical stoichiometry. However, after cleavage, we obtained only the unreacted compound **2**. The same reaction was found to be complete in 6 h by conventional heating. Similar enhancement through microwave irradiation has also been observed during the cleavage step. Compared to conventional thermal hearting, microwave irradiation decreased the reaction time on the support from several hours to several minutes. An excess of isothiocyanates (more than 5 equiv) used to drive reactions to completion complicated final product purification, since removal of unreacted isothiocyanates by precipitation and filtration became very difficult. The cyclization/traceless cleavage step[30] was complete in mildly basic conditions (K_2CO_3) under microwave flash heating for 7 min. The representative library of 3,5-

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Scheme 1. Synthesis of 3,5-Disubstituted 2-Thioxotetrahydropyrimidin-4-ones

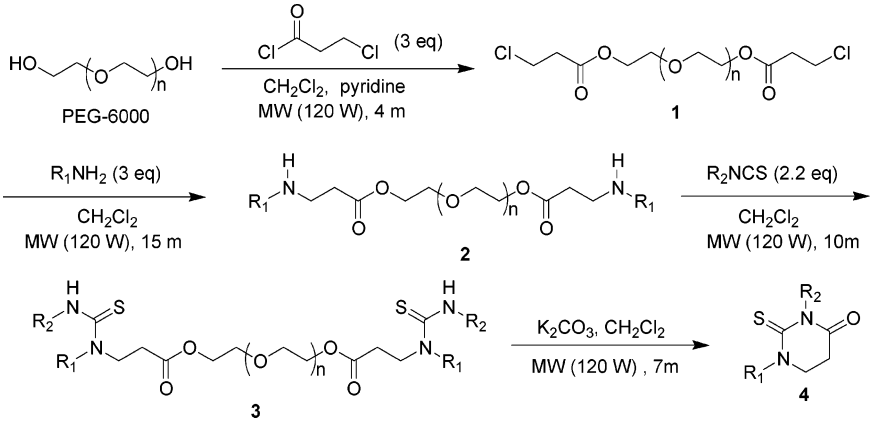
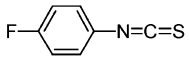
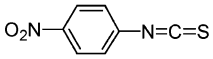
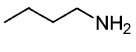
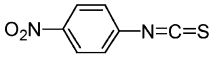
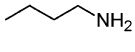
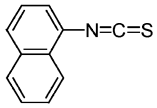
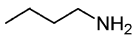
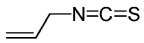
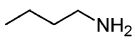
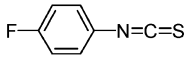
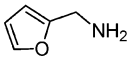
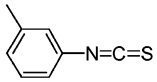
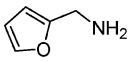
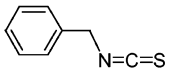
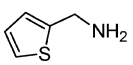
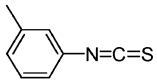
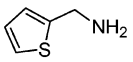
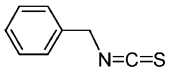
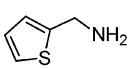
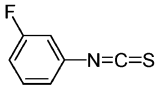
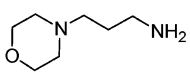
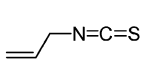
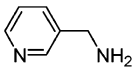
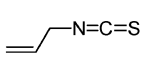
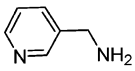
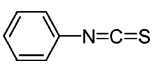
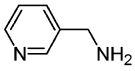
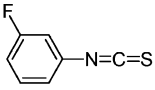


Table 1. Representative Products and Results of Thioxotetrahydropyrimidinones

Entry	R_1NH_2	R_2NCS	LRMS	Crude yield[a]	Purity[b]
4a			266	92	87
4b			293	80	88
4c			307	98	87
4d			312	95	93
4e			226	90	97
4f			280	92	96
4g			300	96	82
4h			300	95	97
4i			316	96	84
4j			316	95	94
4k			320	96	95
4l			297	91	82
4m			261	87	88
4n			297	86	97
4o			311	90	91

[a] Determined on the basis of weight of crude sample (%). [b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm) of crude product (%). Hypersil silica column, 250°4.6 mm, 5 u.

disubstituted 2-thioxotetrahydropyrimidin-4-ones and analytical results are listed in Table 1.

The major advantage of the cyclorelease strategy is the fact that only the desired compound is released into the solution.[30] Upon completion of the reaction, the polymer support was removed from the homogeneous solution to provide the corresponding crude products **4** in 80−98% yield calculated on the basis of the initial loading to the support. The desired compounds were obtained with 82−97% purity as assessed by HPLC (Table 1).[31] The structural characterization of the cleaved libraries demonstrates the success of the major transformations described in Scheme 1. Products from the validated libraries are characterized by mass spectrometry and proton NMR, confirming that in each reaction, the major compound has a molecular ion corresponding to the appropriate product.

In summary, we have successfully combined the advantages of microwave technology with liquid phase combinatorial chemistry to facilitate thioxotetrahydropyrimidinone synthesis. Purification steps are minimized, analytical methods are significantly simplified, and a very defined product is yielded. Microwave irradiation is a powerful tool for accelerating the reaction rate dramatically. It is also worth noting that the polymer-supported intermediates and the polymer support itself remain stable under microwave exposure. The coupling of microwave technology with liquid-phase combinatorial synthesis constitutes a novel and attractive avenue for the rapid generation of structurally diverse libraries.

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(30) For traceless solid-phase synthesis, see: Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607−2624.
(31) All the microwave-assisted polymer-supported reactions described here were performed in a 50-mL round-bottom flask (attached to the reflux condenser) using a CEM Discover Microwave System at a frequency of 2450 Hz (0−300 W). A typical procedure for the synthesis of **4a** (Table 1, entry 1): A mixture of polymer-bound diamine **2a** (600 mg) and 4-fluorophenyl isothiocyanate (2.2 equiv) in 10 mL of dichloromethane was irradiated in a microwave cavity using an output of 120 W for 10 min. Upon completion of the reaction, ethanol (20 mL) was added to the reaction mixture to precipitate out PEG-bound thiourea compound **3a**. The precipitate was then collected on a sintered glass funnel and thoroughly washed with diethyl ethyl (20 mL × 3) following filtration. Finally, the desired cyclized thioxotetrahydropyrimidinones **4a** were released from the support in the microwave cavity using an output of 120 W for 7 min by using K_2CO_3 (3 equiv) in dichloromethane. The

combined filtrate was dried to yield the corresponding crude product **4a**, 3-(4-fluorophenyl)-1-isopropyl-2-thioxotetrahydropyrimidine-4-one, in 92% yield with 87% HPLC purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 1.0 Hz, 1H), 7.10 (bs, 2H), ~5.79 to 5.63 (m, 1H), 3.62 (t, J = 6.6 Hz, 2H), 2.86 (t, J = 6.6 Hz, 2H), 1.29 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 M Hz, $CDCl_3$) δ 180.86, 166.60, 163.80, 160.52, 135.41, 131.11, 130.99, 116.13, 115.82, 53.39, 37.92, 32.08, 19.08; IR (cm^{-1}, neat) 1713, 1644, 1506; mass spectrum (EI) m/z 266 (M^+). Exact mass calcd for $C_{13}H_{15}FN_2OS$: m/z 266.0889. Found 266.0872.

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