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Traceless synthesis of hydantoin by focused microwave irradiation

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Abstract—An efficient, microwave-assisted method for the liquid-phase combinatorial synthesis of 1,3-disubstituted hydantoin has been developed. Chloroacetyl chloride was directly anchored to HO–PEG–OH and subsequently reacted with various primary amines in a microwave cavity. The PEG bound secondary amine coupled with isocyanates and concomitant cyclization–cleavage step occurred in mild basic conditions by microwave flash heating. The desired products were then liberated from the soluble matrix in modest yield and high purity.

Because many potential drug targets have been identified through deciphering protein function with small molecules, there is an urgent need to find efficient ways to synthesize biologically active compounds. Combinatorial chemistry provides a fast access to large quantities of structurally diverse libraries to fuel the chemical genetics. Solid-phase combinatorial synthesis has been successfully developed to overcome tedious work-up, purification problems arising from conventional synthesis.[1,2] However, solid-phase chemistry suffers from various problems such as heterogeneous nature of reaction condition, 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 diverse multifunctional libraries.[3] Liquid-phase synthesis is a complementary type of solid-phase synthesis, since this strategy enables standard solution-based chemistry to be performed with favorable reaction kinetics and product purification 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.

Hydantoin analogs have shown versatile therapeutic applications and some of them have been approved by FDA as drugs.[4–9] For example, Fosphenytoin as a sodium channel antagonist is used for the treatment of epilepsy. Phenytoin has antiarrhythmic, anticonvulsant, and antineuralgic activities. Ethotoin and Mephenytoin both show anticonvulsant effect. Nilutamide is a nonsteroidal orally active antiandrogen in combination with surgical castration for the treatment of stage D2 metastatic prostate cancer (Fig. 1). Moreover, hydantoins also serve as intermediates for producing optically pure

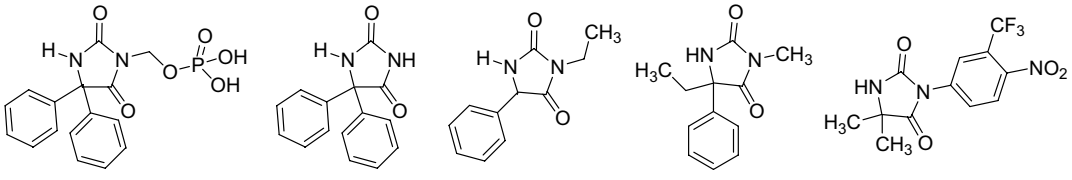

Figure 1. Examples of biologically active hydantoins.

Keywords: Hydantoin; Combinatorial chemistry; Microwave irradiation; Traceless synthesis.
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natural and unnatural α-amino acids, especially in metabotropic receptor research.[10–12]

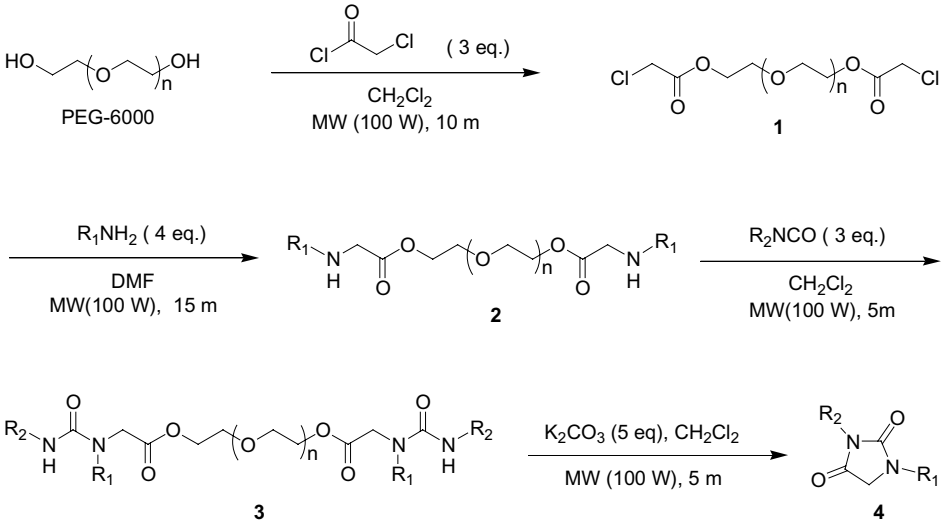
In order to quickly generate a compound library of increasing molecular diversity, it would be favorable to develop methods that combine the expediency of microwave energy with the flexibility of soluble polymer-supported combinatorial chemistry. The practicality of microwave irradiation in chemical reaction enhancement has been recognized for increasing reaction rates and formation of cleaner products.[13] It is clear that the synergistic application of microwave technology to rapidly synthesize biologically significant molecules on the support[14,15] would be of great benefit for accelerated library generation. Although a number of hydantoin synthetic strategies have been reported,[16–26] application of microwave technology to multistep hydantoin synthesis has not been demonstrated. We adapted herein a hybrid strategy using both combinatorial and microwave approach from readily available building blocks to the expeditious synthesis of 1,3-disubstituted hydantoins.

The general synthetic route toward the targeted molecules is given in Scheme 1. Soluble polymer support (HO–PEG–OH, MW∼6000) dissolved in dichloromethane was reacted with chloroacetyl chloride in microwave cavity for 10 min. For comparison to the conventional thermal heating, coupling reaction was also carried out by refluxing methylene chloride (preheated oil bath) for 10 min, using the same stoichiometry. However, the reaction did not proceed at all in the first 10 min time period. Reaction mixtures were purified through a simple precipitation and filtration to remove un-reacted reagents and side products. The same work-up precipitation has been followed at every step of the present reaction sequence. Nucleophilic substitution of polymer immobilized chloroacetyl ester **1** with several primary amines was carried out by microwave exposure (100 W) for 15 min in dimethylformamide. Following solvent washing and drying of PEG bound secondary amines **2**, various isocyanates (3 equiv) were incorporated through microwave irradiation (100 W) within 5 min to give urea intermediates **3**. The large excess of isocyanates used to drive reactions to completion will complicate final product purification. The control reaction was also performed under normal thermal heating in refluxing methylene chloride for 7 h to achieve the same completion. When we compared both MW results and conventional pre-heated oil bath results, we observed that there is a clear improvement in yield and reaction time by using MW heating. A similar enhancement was also observed in other steps of the current reaction sequence.

The cyclization-assisted cleavage of polymer support combined linker cleavage and ring formation in one-step was conducted in mild basic conditions (K_2CO_3) with 100 W microwave flash heating for 5 min. The representative library of 1,3-disubstituted hydantoins and analytical results are listed in Table 1.[27]

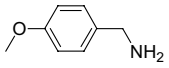
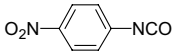
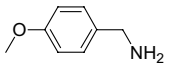
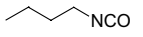
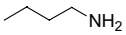
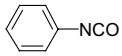
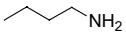
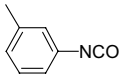
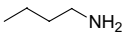
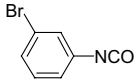
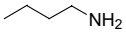
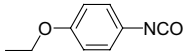
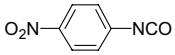
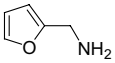
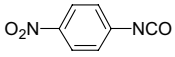
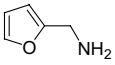
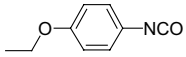
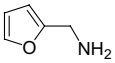
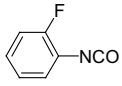
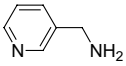
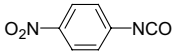
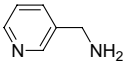
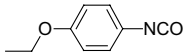
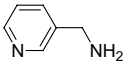
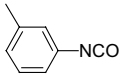
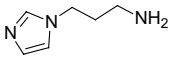
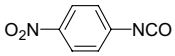
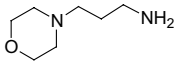
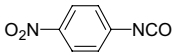
The major advantage of cyclorelease strategy is the fact that only the desired compound is released into the solution.[28] Upon completion of the reaction, the polymer support was removed from the homogeneous solution by precipitation and filtration to provide the corresponding crude products **4** in 70–94% yield calculated on the basis of the initial loading to the support. The desired compounds were obtained with 83–97% purity as assessed by HPLC (Table 1). Structural characterization of 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



Scheme 1. Microwave-assisted synthesis of hydantoin on soluble polymer support.

Table 1. Representative products and results of hydantoins

Entry	R_1NH_2	R_2NCO	LRMS	Yield[a]	Purity[b]
4a			341	88	91
4b			276	86	96
4c			232	90	86
4d			246	93	96
4e			310	89	95
4f			276	83	97
4g			263	90	96
4h			301	81	97
4i			300	70	92
4j			274	80	83
4k			312	94	96
4l			311	76	96
4m			281	78	94
4n			329	71	97
4o			348	70	95

[a] Crude yields determined by weight of crude sample (%).
[b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm), Hypersil silica column, 250×4.6 mm, 5 μ.

combinatorial chemistry to optimize 1,3-disubstituted hydantoins synthesis. Purification steps are minimized, analytical methods are significantly simplified and very defined products are yielded. Microwave irradiation is a powerful tool for accelerating reaction rate dramatically. Compared to conventional thermal heating, microwave irradiation decreased the reaction time on the support from several days to several minutes. It is also worth noting that the polymer-supported intermediates and 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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27. All the microwave-assisted polymer-supported reactions described here were performed in a 50 mL round bottom flask (attached to the reflux condenser) with 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** (746 mg) and 4-nitrophenyl isocyanate (3 equiv) in 10 mL of dichloromethane was irradiated under a microwave cavity with an output at 100 W for 5 min. Upon completion of reaction, ether (30 mL) was added to the reaction mixture at ice-water bath to precipitate out PEG-bound urea compound **3a**. The precipitate was then collected on a sintered glass funnel and thoroughly washed with diethyl ethyl (10 mL × 3) following filtration. Finally, the desired hydantoin **4a** was released from the support in the microwave cavity with an output at 100 W for 5 min by using K_2CO_3 (5 equiv) in dichloromethane. The same work-up procedure has been followed by precipitation to separate the desired product and polymer support. The combined filtrate was dried to obtain **4a** in 88% crude yield calculated on the basis of the initial loading to the support. 1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-imidazolidine-2,4-dione **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, $J = 9.3$ Hz, 2H), 7.77 (d, $J = 9.3$ Hz, 2H), 7.25 (d, $J = 8.7$ Hz, 2H), 6.29 (d, $J = 8.7$ Hz, 2H), 4.6 (s, 2H), 3.93 (s, 2H), 3.82 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.0, 159.8, 154.4, 146.3, 137.6, 129.9, 126.7, 125.7, 124.3, 114.5, 55.4, 48.8, 46.5; MS (FAB$^+$) m/z 342 (M+1).
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