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Microwave-assisted traceless synthesis of thiohydantoin

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Abstract—An efficient, microwave-assisted method for the liquid-phase combinatorial synthesis of 3,5-disubstituted-thiohydantoin has been developed. Fmoc-protected amino acids were coupled with HO-PEG-OH and after deprotection, reacted with various isothiocyanates in microwave cavity. The PEG bound thiourea compounds underwent base mediated cyclization/cleavage step by microwave flash heating. The desired products were then liberated from the soluble matrix in good yield and purity under microwave exposure.

With more and more therapeutic targets emerging from chemical genomics research, combinatorial chemistry provides a fast access to the structurally diverse libraries to fuel the chemical genetics. Limitations in efficiency of classical chemical synthesis resulting from tedious work-up and purification after each reaction step can be overcome by the solid phase synthesis due to advantages like easy and fast purification.[1] It is expected that solid phase library synthesis, using known solution-phase reaction conditions, will be useful to identify novel therapeutics.[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 construction of diverse multifunctional libraries.[3] This strategy enables standard solution-based chemistry to be utilized, and product purification is just like that of solid phase reactions. Furthermore, monitoring progress of reactions on the support is significantly simplified by using conventional analytical methods such as NMR, IR, HPLC and TLC.[4]

Recently combinatorial organic synthesis has focused on the generation of non-peptide small molecules with potential therapeutical value. Compounds with hydantoin structural motif have been identified to display a wide range of biological activities (Fig. 1). For example, phenytoin has many usages, such as antiarrhythmic, anticonvulsant, antineuralgic, trigeminal neuralgia and skeletal muscle relaxant.[5,6] Sulfahydantoin has been studied on the respect of inhibition of serine proteases.[7,8] The glucopyranosylidene-spiro-thiohydantoin is reported as an efficient inhibitor of muscle and liver glycoen phosphorylases.[9,10]

Microwave irradiation in chemical reaction enhancement has been well recognized for increasing reaction rates and formation of cleaner products.[11] In order to quickly generate compounds of increasing molecular diversity, the synergistic application of microwave technology to rapidly synthesize medicinally interesting molecules on the support would be of great benefit for accelerated library generation.[12,13] Although a number of strategies for synthesis of hydantoin analogs have been reported,[14–28] application of microwave technol-

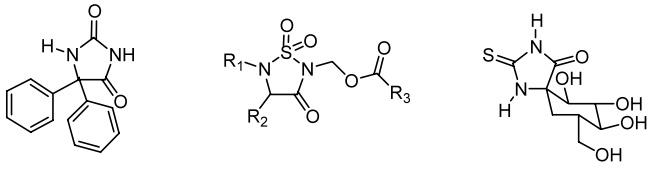

Figure 1. Examples of medicinally interesting hydantoin analogs.

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ogy to facilitate multi-step thiohydantoin synthesis is unknown. We adopted herein a hybrid strategy using both combinatorial and microwave approach from readily available building blocks to the expeditious synthesis of thiohydantoin derivatives.

The general synthetic route of thiohydantoins is given in Scheme 1. Soluble polymer support (HO-PEG-OH, MW $\sim$6000) dissolved in CH_2Cl_2 was coupled with Fmoc-protected amino acids under DCC/DMAP activation by focused microwave reactor (150 W) for 14 min. For the comparison to the conventional thermal heating, coupling reactions were also carried out in refluxing methylene chloride (preheated oil bath) for 14 min, using the same stoichiometry. However, the reaction did not proceed at all in the first 14 m time period. Reaction mixtures were purified through a simple precipitation, filtration and solvent washing to remove un-reacted reagents and side products. The same work-up precipitation has been followed at every step of the present reaction sequence. Following deprotection of compound **1** with 10% piperidine in methylene chloride at room temperature, various isothiocyanates were introduced through 150 W microwave irradiation for 7 min in methylene chloride to give thiourea intermediate **3**. The control reaction was also performed under normal thermal heating in refluxing methylene chloride (preheated oil bath) for 7 min, using identical stoichiometry. However, after cleavage we obtained only the unreacted compound **2**. The same reaction was found to complete in three hours.

The cyclization/traceless cleavage step[30] was complete under mild basic condition (K_2CO_3) with 150 W microwave flash heating for 7 min. The representative library of thiohydantoins and analytical results are listed in Table 1.

The major advantage of cyclorelease strategy is the fact that only the desired compound is released into the solution.[29] Upon completion of reaction, polymer support was removed from the homogeneous solution to provide the corresponding products **4** in 88–99% yield based on the initial loading to the support. The desired compounds were obtained with 81–99% purity as assessed by HPLC (Table 1). The 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 combinatorial chemistry to facilitate high-speed 3,5-disubstituted thiohydantoins synthesis. Purification steps are minimized, analytical methods are significantly simplified and well defined products are yielded. Microwave irradiation is a powerful tool for accelerating reaction rate dramatically. Compared to conventional thermal hearting, microwave irradiation decreased the reaction time on the support from several days to several minutes. It should be stressed 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.

Acknowledgements

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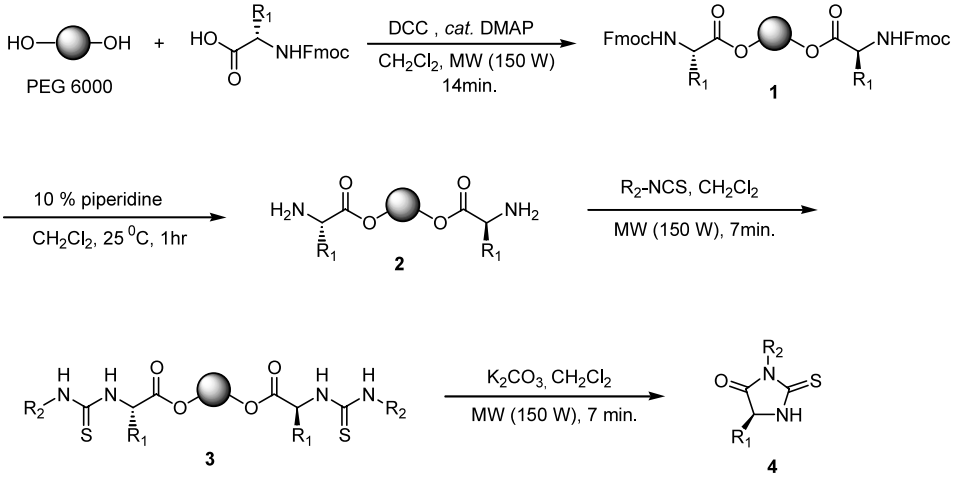
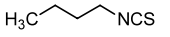
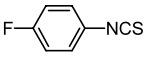
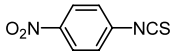
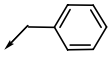
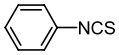
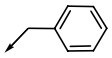
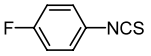
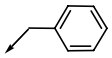
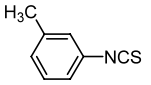
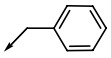
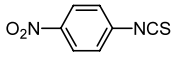
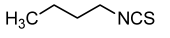
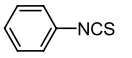
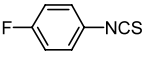
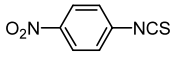
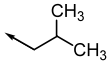
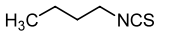
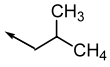
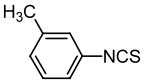
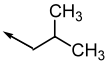
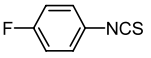


Scheme 1. Synthesis of 3,5-disubstituted thiohydantoins.

Table 1. Representative products and results of 3,5-disubstituted thiohydantoins

Entry	R_1	R_2	LRMS	Crude yield[a]	Crude purity[b]
4a	H		172	90%	81%
4b	H		210	95%	96%
4c	H		237	92%	89%
4d			282	96%	96%
4e			300	95%	90%
4f			296	97%	97%
4g			327	94%	97%
4h			214	88%	87%
4i			234	97%	99%
4j			252	94%	96%
4k			279	99%	99%
4l			228	96%	91%
4m			262	90%	99%
4n			266	97%	99%

a: Determined based on weight of crude sample (%).
b: Purity determined by HPLC analysis (UV detection at λ= 254nm) of crude product (%).
Hypersil silica column, 250 x 4.6 mm, 5u

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30. All the microwave-assisted polymer-supported reactions described here were performed in a 100 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** (600 mg) and *n*-butyl isothiocyanate (3.0 equiv.) in 5 mL of CH_2Cl_2 was irradiated under microwave cavity with an output at 150 W for 7 min. Upon completion of reaction, ether (20 mL) was added to the reaction mixture to precipitate out PEG-bound thiourea compound **3a**. The precipitate was then collected on sintered glass funnel and thoroughly washed with diethyl ether (3×20 mL) following filtration. Finally, the desired cyclized thiohydantoin **4a** was released from the support in microwave cavity with an output at 150 W for 7 min by using K_2CO_3 (3 equiv.) in dichloromethane. The combined filtrate was dried to offer the corresponding crude product **4a**, 3-butyl-2-thioxoimidazolidin-4-one, in 90% yield with 81% HPLC purity: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06–4.03 (m, 2H), 3.81 (t, J = 7.5 Hz, 2H), 1.70–1.60 (m, 4H), 1.27–1.23 (m, 3H); ^{13}C NMR (75 M Hz, $CDCl_3$) δ 183.25, 171.51, 48.34, 41.25, 29.63, 20.03, 13.68; IR (cm^{-1}, neat) 2956, 2911, 1713, 1506, 1434, 1345; MS (EI) m/z 172 (M^+).