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Microwave-assisted solid-phase synthesis of hydantoin derivatives

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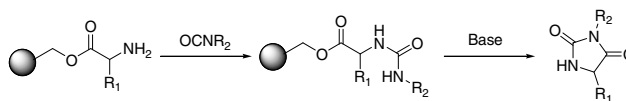
Abstract—A microwave-assisted synthesis of 3,5- and 1,3,5-substituted hydantoins starting from various resins for solid-phase combinatorial chemistry has been developed. The hydantoins were synthesized from pre-loaded resins with amino acids via treatment with isocyanate or phenylisocyanate and subsequent intramolecular cyclization. Both reactions were performed under microwave irradiation. We studied the cyclative cleavage leading to hydantoin compounds dependent on the nature of the amino acid and the nucleofuge properties of the resin.

Hydantoin moiety constitutes an attractive pharmacological scaffold present in several drugs.¹ This small and rigid heterocyclic backbone, presenting three points of diversity, could act on various pharmacological targets. Especially, hydantoin nucleus could be found in a broad range of biological active compounds displaying neuroprotective, antiarrhythmic, anticonvulsant, anti-hypertensive, anti-inflammatory, analgesic, antidiabetic, antiandrogen, antibacterial, antiviral, antifungal, or diuretic activities as well as herbicidal or fungicidal properties.^{2–10} Various alkaloid compounds from marine organisms or bacteria contain also an hydantoin moiety.¹ Moreover, hydantoins are the key intermediates during the synthesis of optically pure natural and unnatural amino acids especially those involved on metabotropic ligands.^{11–13}

In order to quickly generate large libraries of hydantoins, we expected that the combination of the solid-phase tool and the microwave technology will be useful for the development of efficient methodologies for the production of hydantoin scaffolds for drug discovery. Microwave irradiation technology in organic synthesis has now become an integrated part of combinatorial chemistry and drug discovery process.^{14–19} Microwave irradiation heats the reaction contents directly by taking advantage of the ability of some liquids and solids to

transform electromagnetic radiation into heat. The short reaction times and expanded reaction range offered by microwave-assisted chemistry in conjunction with the well-known advantages of solid-phase chemistry could allow us to generate hydantoin leads efficiently. Although several synthetic methods are described for the preparation of hydantoin libraries, including microwave-assisted liquid-phase combinatorial synthesis, none of them combines solid-phase and microwave synthesis, to the best of our knowledge.^{1,20,21} The novel part of this paper is the use of microwave energy/heating, but combined with solid-phase technology this would have to be the most efficient route in terms of reaction time taken, product purity, and yield that can be achieved.

Since the first report of solid-phase synthesis of hydantoin libraries by DeWitt et al.,²² several synthetic methods have been developed on resins or PEG.^{23–27} We were especially interested by base-catalyzed cyclative cleavage strategies allowing both cyclization and cleavage in one step.²⁸ The hydantoin formation via solid-phase intramolecular cyclization is well represented in the literature. The major advantage of this strategy resides in the fact that products which are not capable of cyclization remain attached to the solid support leading



Scheme 1.

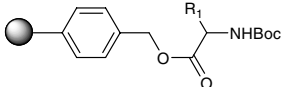
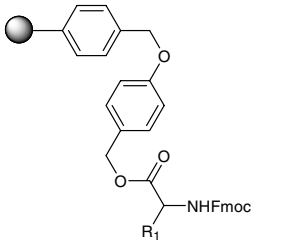
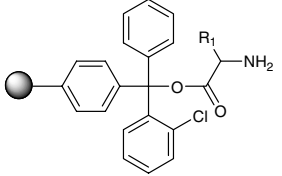
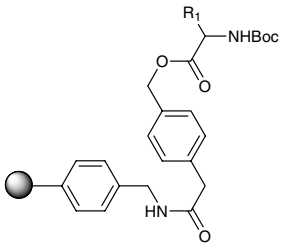
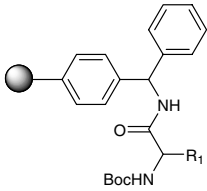
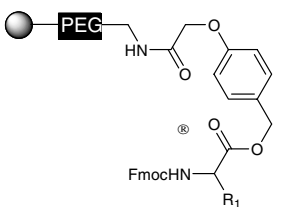
Keywords: Hydantoin; Solid-phase synthesis; Microwave irradiation; Cyclative cleavage.

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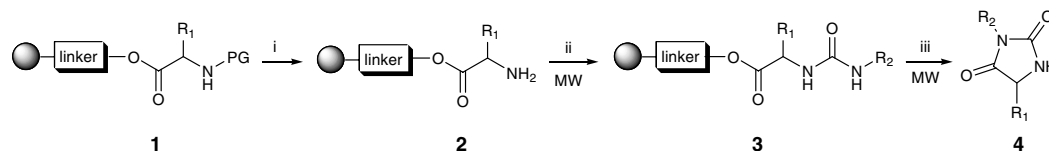
generally to highly pure compounds. The rate of cyclization is then dependent on the nature of the side chains R_1 and R_2 attached to the cyclic compound in formation, but also dependent on the nucleofuge property of the resin under the same basic conditions (Scheme 1).

For the synthesis of hydantoin libraries on solid support, one of the most powerful methods could be the use of commercially available pre-loaded resins with N-protected amino acids. Suitable N-deprotection of the amino acid followed by reaction of the resin with

Table 1. Hydantoins produced via Scheme 2

Entry	Resins (1)	aa (R_1)	R_2	Yield % (4) ^a
1	 Boc-aa-Merrifield resin	Phe	Ph	95
		Phe	H	90
		Ala	Ph	90
		Val	Ph	75
		Glu(OBz)	Ph	85
		Ile	Ph	80
2	 Fmoc-aa-Wang resin	Gly	Ph	70
		Phe	Ph	100
		Phe	H	90
		Ile	Ph	85
		Val	Ph	80
		Leu	Ph	75
		Ala	Ph	75
		Pro	Ph	90
		Glu(<i>Or</i> -Bu)	Ph	95
		Glu(<i>Or</i> -Bu)	H	90
		3	 aa-2-CITrt resin	Pro
Glu(<i>Or</i> -Bu)	Ph			75
4	 Boc-aa-PAM resin	Ala	Ph	60
5	 Boc-aa-MBHA resin	Ala	Ph	10
6	 Fmoc-aa-NovaSyn TGA resin	Glu(<i>Or</i> -Bu)	Ph	40

^a Yields determined by weighing of crude sample (95–100% purity determined by HPLC analysis).



Scheme 2. Reagents and conditions: (i) 20% piperidine in DCM, 20 min, rt or 50% TFA in DCM, 1 h, rt, then Et₃N, (ii) R₂NCO, THF, MW irradiation power 300 W, 10 min; and (iii) Et₃N, THF/DMF (4:1 v/v), MW irradiation power 300 W, 15 min.

an isocyanate could generate the corresponding urea (Scheme 1). Treatment of this intermediate with a base leads to nucleophilic attack on the ester (or amide) allowing the release of the hydantoin product. Under these basic conditions, urea will undergo cleavage, while unreacted amino acid will remain on the support.^{21,23,24,26,27,29–32} After cleavage, only the desired product is released in the solution, therefore facilitating significantly the purification step.

In order to determine the most suitable resin for such transformation under microwave heating, we studied and compared the performance of various resins under the same microwave conditions. For this purpose, reactions were performed using various combinations of resins, spacers, linkers, or amino acids (Table 1). The general synthetic route toward the targeted molecules is shown in Scheme 2. After N-deprotection of the anchored amino acid (Boc or Fmoc protecting group, except in the case of aa-2-CITrt resin, entry 3) at room temperature, the two other steps were carried out under microwave conditions using a single mode cavity synthesizer to ensure reproducibility. At each step, the reaction conditions were optimized under microwave irradiation using various experimental conditions such as temperature, reaction time, power of the irradiation, solvent, and concentration of starting materials. The reaction progress was monitored by IR of the resin (urea FTIR at 1656 cm⁻¹) and by LC/MS and ¹H NMR analyses of the final hydantoin. The treatment of the free amine moiety of the solid-phase bound amino acid (1.0 g, 0.76 mmol, 0.76 mmol/g) with isocyanate (3.04 mmol) was achieved in THF (5 mL) in a microwave reactor at 60 °C for 10 min. A control reaction for isocyanate coupling was performed in parallel, at room temperature in THF, for 10 h to achieve the same completion. The resin was then washed, dried and treated with Et₃N (0.43 mL, 3.04 mmol) in THF/DMF (5 mL, 4:1 v/v) in a microwave reactor at 110 °C for 15 min. Higher temperatures did not give any additional improvements. A control reaction for cyclative cleavage was also performed under normal thermal heating in refluxing THF for 12 h to achieve the same completion. Under optimal conditions, hydantoin was obtained from 2 in 25 min instead of 22 h under conventional well-known conditions.

This general protocol³³ could be applied to all the previously described pre-loaded resin with an ester linkage between the amino acid and the resin (Table 1, entries 1–4) allowing the synthesis of a library of various hydantoin with good to excellent yields. We were able to provide for a diverse set of amino acids, heterocyclic compounds with yields in the same order to conven-

tional solid-phase synthesis. All the tested resins were found to resist under microwave irradiation. However, the amide bound resins, less sensitive to cleavage due to their poor nucleofuge potential, released hydantoin compounds with lower yields (Table 1, entries 5 and 6). We reasoned that an ester linkage is more suitable for cyclative cleavage, following our general basic protocol under microwave irradiation.

The results from the solid-phase synthesis of hydantoin by cyclorelease strategy clearly demonstrate that microwave irradiation offers an effective and attractive technique to produce a library of hydantoin with short reaction times, in high yields, and with high purity compared to conventional classic thermal described in the literature. Microwave-assisted heating should prove highly practical for combinatorial solid-phase synthesis of hydantoin or other heterocyclic scaffolds.

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33. *General procedure for the synthesis of hydantoins.* All the microwave-assisted reactions were performed at 300 W in a 20 mL vial with a Biotage Initiator 60 EXP[®]. Temperature was measured with an IR sensor on the outer surface of the reaction vial.
After suitable conventional N-deprotection of the pre-loaded resin **1**, the resulting DCM-swollen resin **2** (1.0 g, 0.76 mmol, 0.76 mmol/g) was treated with isocyanate (3.04 mmol) in THF (5 mL) in a microwave reactor at 60 °C for 10 min. The solvent was removed by filtration and the resin was washed with THF (2 × 10 mL), DMF (2 × 10 mL), MeOH (2 × 10 mL), DCM (2 × 10 mL), and dried. This resin **3** was then treated with Et₃N (0.43 mL, 3.04 mmol) in THF/DMF (5 mL, 4:1 v/v) in a microwave reactor at 110 °C for 15 min. The solvent was removed by filtration and the resin was washed with THF (2 × 10 mL) and DCM (2 × 10 mL). Combined filtrates were dried to obtain the desired product **4** in a crude yield calculated on the basis of the initial loading support.