Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4603-4606, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00986-6

Solid Phase Synthesis of Hydantoin Library Using a Novel Cyclization and Traceless Cleavage Step

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Abstract: *The variety of N,N-disubstituted hydantoin libraries were constructed using derivatives of amino acids, aromatic aldehydes, and isocyanates. The cyclization step of hydantoin was a novel, fast, and clean reaction and completed within five minutes to 1 hour with neat diisopropylamine. All library compounds were obtained in excellent yield with high purity even after 5 steps.*
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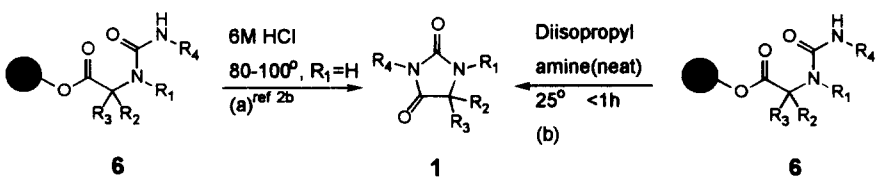
The emergence of combinatorial chemistry leads new powerful means of the generation of a variety of molecular diversity.[1] Recently, combinatorial organic synthesis has been focused on the generation of non-peptidic small molecules such as benzodiazepines[2], β-lactams[3], β-turn mimetics[4], quinazoline[5], and tropanes.[6] These molecular diversities based on the solid phase combinatorial organic synthesis are being used for a rapid lead generation in drug discovery and the developement of biologically active compounds with potential therapeutic value.[7] Hydantoin derivatives are attractive targets for drug discovery because of their biological behavior.[8]

The first solid phase synthesis of hydantoin libraries was reported by Hobbs DeWitt in which cyclization was performed on solid support through a C-terminal ester linkage (Scheme I, a).[2b] They employed toxic aqueous hydrochloric acid (6M) at high temperature (85-100°) for 2 hours to cyclize and cleave the final hydantoins from the solid support. Although basic condition was first reported by Dressman[9] using triethylamine to cyclize hydantoins on solid phase, it had some inconveniences. First, laborious solution chemistry was needed to make diversified amino acid building blocks and long reaction time (2 days) with excess N,O-bis(trimethylsilyl)acetamide was required for the synthesis of the precursor.

Scheme I

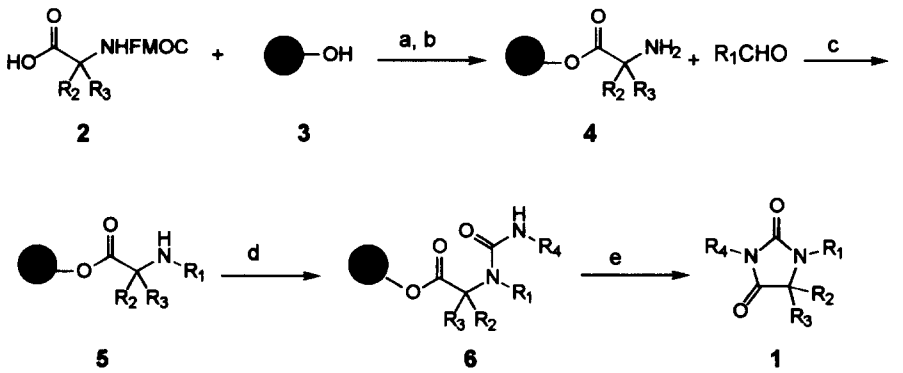


Second, they used medium to high temperature (55-90 °C) for the cyclization to the desired products. Those harsh conditions might limit the utility of this methodology. We developed a new procedure for the cyclization of hydantoin library by employing neat diisopropylamine at room temperature (Scheme I, b). This

method was fast (less than 1 hour), convenient, mild, and afforded high yield and purity.

The general synthetic procedure of hydantoin derivatives is outlined in Scheme II. We followed the conventional solid phase synthesis. The coupling reaction between Wang resin[10] and amino acid derivative

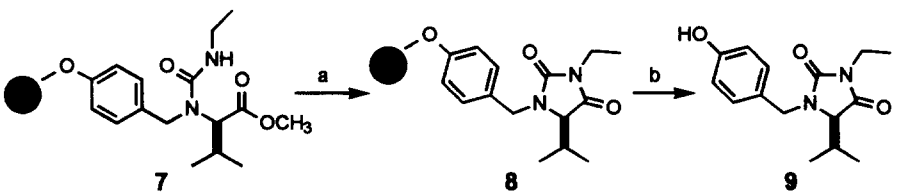
Scheme II



Conditions: a) DIC, DMF, DMAP, 12h; b) 20% piperidine, DMF, 1h; c) i) DMA, 1% AcOH, 5h, ii) $NaBH_3CN$; d) R_4NCO, DMF/toluene (1:1v/v); e) diisopropylamine (neat), rt, <1h.

was quantitative (>95%) (loading capacity was 0.81 mmol/g compared to the starting 0.85mmol/g). Imine was formed with 3.5eq. aromatic aldehyde in 1% acetic acid solution of DMA. After 5 hours of stirring, 5eq.

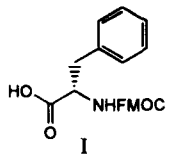
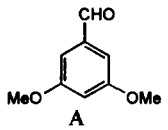
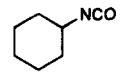
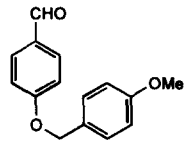
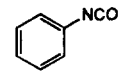
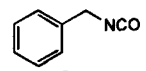
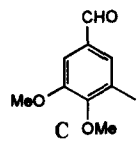
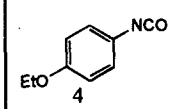
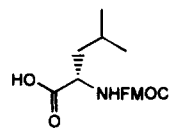
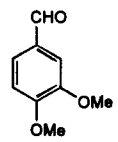
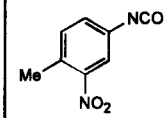
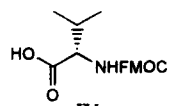
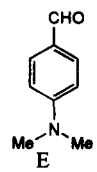
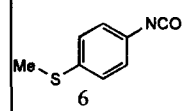
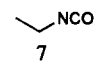
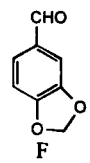
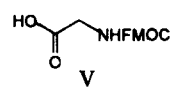
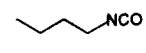
Scheme III



Conditions: a) diisopropylamine (neat), rt, <1h. b) 30% TFA in CH_2Cl_2.

$NaBH_3CN$ was added and the reaction mixture was kept stirring for 24 hours.[11,12] Treatment of the corresponding resin-bound secondry amine **5** with 3.5eq. isocyanate in DMF/toluene (1:1 v/v) solution for 5 hours gave the resin-bound carbamate **6**. We tested several amines and it turned out that triethylamine, pyrrolidine, and piperidine worked as efficiently as diisopropylamine but pyridine showed no sign of cyclization. We preferred to use diisopropylamine due to its convenience of removal. Upon treatment of neat diisopropylamine for 5 minutes to 1 hour,[13] hydantoin derivatives were formed in high yield (Table 1)

Table 1. The hydantoin libraries using amino acids, aromatic aldehydes, and isocyanates

	R_1	R_4	Product[a]	Yield[b]
 I	 A	 1	IxAx1[c]	89
			IxCx2	92
	 B	 2	IxEx3	89
			IxFx4	89
 II			IxAx6	91
		 3	IxBx7	85
	 C		IIxAx1	89
		 4	IIxFx2	92
 III			IIxAx8	86
	 D		IIIxAx2	91
		 5	IIIxAx6	82
			IVxAx4	87
 IV	 E	 6	IVxBx7	89
			IVxDx8	90
			VxAx1	86
		 7	VxCx1	93
	 F		VxEx4	82
 V		 8	VxFx7	87

[a] All compounds were synthesized in high purity. [b] All yields correspond to column chromatography purified materials and are relative to the initial loading. [c] Combination of phenylalanine I, 3,5-dimethoxybenzaldehyde A, and cyclohexyl isocyanate 1.

with remarkable purity.[14]

The generality of this methodology was verified by the synthesis of other hydantoin derivatives such as **9** (Scheme III). Under the same cyclization condition, **9** was obtained in high yield and purity which was comparable to that of **1**.

Summary,

We constructed 400 hydantoin libraries with an efficient route using solid phase synthesis in which neat diisopropylamine was employed for a novel cyclization/traceless cleavage step. Biological activities of the hydantoin libraries are under investigation. The synthesis of other classes of hydantoin libraries will be published separately.

Acknowledgment. We would like to thank Dr. Wonjae Lee for analytical support and Dr. Hyun Ik Shin for constructive comments during the preparation of this manuscript.

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11. Kaiser test showed negative result.
12. We observed 89% ee by chiral HPLC after cleavage from resin.
13. No racemization was observed during the cyclization step.
14. Each compound showed single spot and one peak on TLC and HPLC, respectively.

(*Received in Japan* 19 *March* 1997; *revised* 15 *May* 1997; *accepted* 16 *May* 1997)