Pergamon

Tetrahedron Letters 39 (1998) 3379–3382

TETRAHEDRON LETTERS

Microwave-Promoted Reactions: Intramolecular Carbanilide Cyclization to Hydantoins Employing Barium Hydroxide Catalyst.

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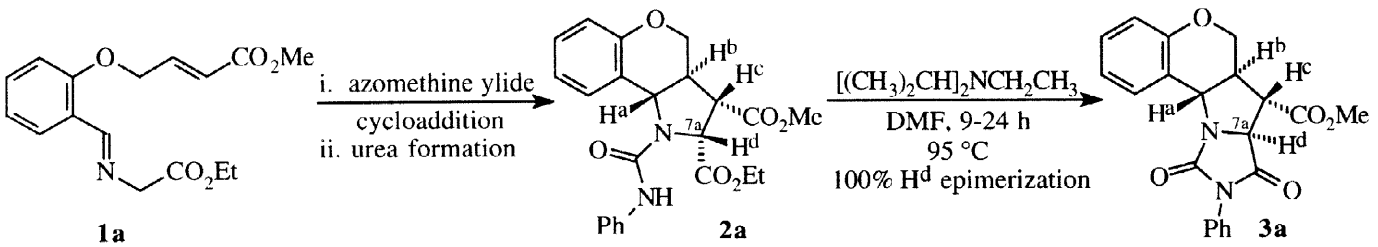
Received 23 January 1998; revised 23 February 1998; accepted 25 February 1998

Abstract: *Hydantoin ring formation via carbanilide cyclization is achieved in high yield with short reaction time by employing catalytic amounts of $Ba(OH)_2$ (anhydrous or octahydrate) in DMF under microwave irradiation. Evidence is provided that kinetic product* ***4*** *(trans,anti,cis stereochemistry) epimerizes to thermodynamic product* ***3*** *(trans,anti,trans stereochemistry).*

The hydantoin moiety imparts a broad range of biological activities with both medicinal (cf., anticonvulsant)[1] and agrochemical (cf., fungicidal and herbicidal)[2] applications. Given this utility, it is not surprising that a large number of hydantoins adorned with diverse substituents have been synthesized.[3]

In previous studies, we developed a novel route to hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole derivatives by sequential azomethine ylide cycloaddition (→ proline) and carbanilide cyclization (→ hydantoin) chemistry.[4] This strategy delivered polycyclic hydantoin targets with stereoselective control of the four contiguous pyrrolidine stereocenters, but formation of the hydantoin moiety required long reaction times, high temperature, and excess base. Indeed, the forcing conditions required for carbanilide cyclization in these studies resulted in some thermal decomposition of product. This carbanilide formation step, outlined in **Scheme 1**, delivered (*trans,anti,trans*)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole **3a** as a single isomer implying that the key 1,3-dipolar cycloaddition step proceeded via an *endo*-like transition state and that C_{7a} epimerization occurred during the carbanilide cyclization step (**2** → **3**).[5]



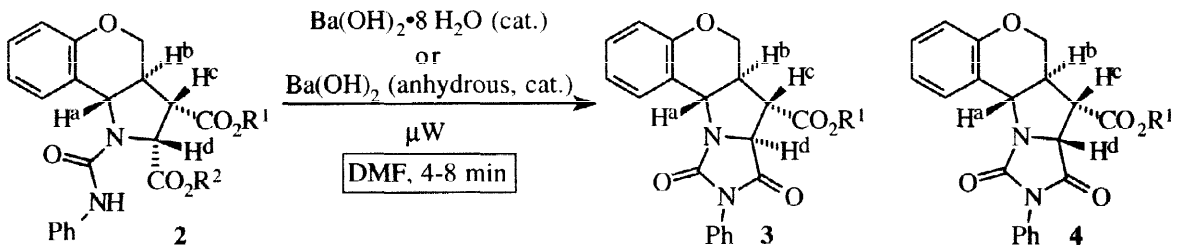
1a **2a** **3a**

Scheme 1.

0040-4039/98/$19.00
PII: S0040-4039(98)00497-3

Following the pioneering work of Gigure and Gedye,[6] microwave (μW) applications in organic chemistry have become more prevalent.[7] The principal advantages of μW mediation are reaction acceleration and accompanying minimization of thermal decomposition products. No doubt, improvements in the design of continuous μW reactors[8] will further advances in this area.

A number of examples of heterocycle formation under μW conditions can be found in the literature[9] and herein we report an examination of carbanilide cyclizations[10] under μW mediation using a MICROWELL-10 REACTOR.[11] We have found that reaction **2** → **3** proceeds efficiently in high yield at ambient pressure within minutes by employing a catalytic amount of $Ba(OH)_2$ (anhydrous or octahydrate) in DMF under μW irradiation (**Scheme 2**).



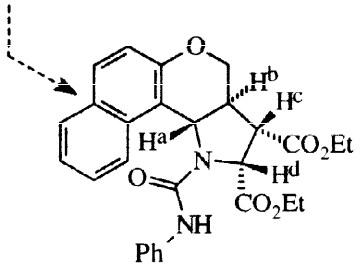
Scheme 2.

In a typical procedure, carbanilide **2a** (R^1 = Me, R^2 = Et; 40 mg, 9.75 x 10^{-2} mmol) and $Ba(OH)_2 \cdot 8H_2O$ (6.1 mg, 1.95 x 10^{-2} mmol) were dissolved in DMF (1.0 mL) in a teflon-capped test tube which was placed in a MICROWELL-10 REACTOR and irradiated for 7.5 minutes (three 2.5 min intervals with cooling to room temperature between intervals) at 30W. The reaction mixture was quenched with 10% aq. citric acid (10 mL) and extracted with EtOAc (25 mL x 2). The combined organic solution was washed with water (15 mL x 3), dried ($MgSO_4$), and concentrated. Flash column chromatography (SiO_2, EtOAc: hexanes::3:7) gave pyrroloimidazole **3a** (33.6 mg, 8.9 x 10^{-2} mmol, 91% yield).

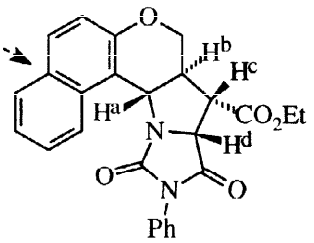
Our preparative results are summarized in the **Table**. Reaction of **2a** with anhydrous $Ba(OH)_2$ (cat.) under low μW power and short reaction time (3 min) produced a mixture of kinetic product **4a** and thermodynamic product **3a** along with starting material **2a** (entries 1-3).[12] In the case of **5** (entry 4), only kinetic product **6** (i.e., *trans,anti,cis* stereochemistry) was produced in high yield under both μW and thermal reaction conditions (note: H^d-epimerization would lead to a strong non-bonding interaction between the hydantoin and naphthalene moieties). In order to achieve full generation of **3a**, a longer reaction time (7.5 min) was required (entries 5-7). Indeed, both urea esters (R^2 = Et, Bn) investigated cyclized in high yield to the corresponding epimerized pyrroloimidazole **3** upon μW irradiation at 30W for 7.5 min.

Table

entry	R^1	R^2	μW conditions time (min)/W	ratio **3**[a]:**4**[a]	yield[b] (%)	thermal conditions time (h)/yield (%)
1 (**2a**)	Me	Et	3 min[c] / 20W	53:47	44[d]	- -
2 (**2b**)	Et	Et	3 min[c] / 20W	52:48	40[d]	- -
3 (**2c**)	Et	Bn	3 min[c] / 20W	57:43	58[d]	- -
4 (**5**)			2.5 min / 30W	0:100	94	- -
5 (**2a**)	Me	Et	7.5 min[e] / 30W	100:0	91	24 / 82
6 (**2b**)	Et	Et	7.5 min[e] / 30W	100:0	84	24 / 78
7 (**2c**)	Et	Bn	7.5 min[e] / 30W	100:0	81	9 / 96

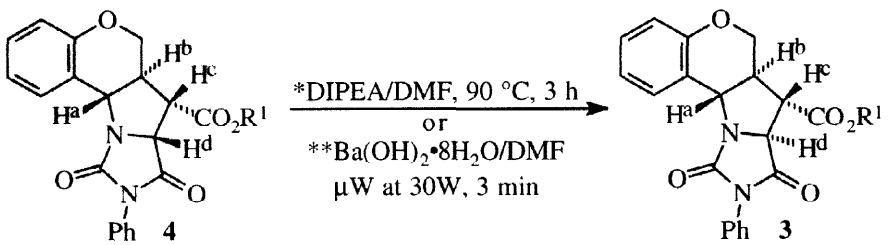


(6)



[a]Compounds **3a** (R^1 = Me), **3b** (R^1 = Et), **4a** (R^1 = Me), **4b** (R^1 = Et), and **6** were identified by single crystal X-ray analysis. [b]Sum of the total yield of **3** + **4**. [c]Three 1 min intervals with cooling to 0 °C between intervals. [d]These reactions were quenched before complete conversion of starting material to maximize **4**. [e]Three 2.5 min intervals with cooling to room temperature between intervals.

We next examined H^d-epimerization **4** → **3** both with *N,N*-diisopropylethylamine/DMF under thermal conditions (90 °C) and with $Ba(OH)_2 \cdot 8H_2O$/DMF under μW irradiation. As depicted in **Scheme 3**, epimerization of **4a** and **4b** proceeds smoothly to give thermodynamic products **3a** and **3b**, respectively. Again, H^d-epimerization does not take place in **6** under either thermal or μW conditions.



Scheme 3

	R^1	Δ **yield***	μW **yield****
4a → **3a**	Me	86%	85%
4b → **3b**	Et	85%	87%

5 ⇸ **6**

In conclusion, μW-mediated carbanilide cyclization occurs with reduced reaction time (μW minutes vs. Δ hours). The present work has also firmly established the interplay between *endo*-selectivity in the azomethine ylide cycloaddition step and H^d-epimerization during the carbanilide cyclization step in stereoselective delivery of pyrroloimidazoles. As discussed above, the key to successfully executing this μW reaction was the use of catalytic $Ba(OH)_2$ in DMF solvent.[13]

Acknowledgment: We thank the National Science Foundation and Novartis Crop Protection AG for financial support of this research. We also thank the LabWell Inc. for providing the MICROWELL-10 REACTOR.

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11 MICROWELL10 REACTOR consists of a μW control unit (0-500W), a time control unit (0-100 min), and a power supply (600W).

12 In order to maximize kinetic product **4a**, this reaction was quenched prior to complete consumption of starting material **2a**.

13 We examined various bases (Et_3N, DIPEA, NaH, NaOH, KH, ^tBuOK, LiOH, $BaCO_3$), Lewis acids ($MgCl_2$, $BaCl_2$, LiCl), and solvents (benzene, toluene, DMSO, ethanol, diglyme, dimethoxy ethane). We believe catalytic $Ba(OH)_2$ in DMF provides the best conditions for this intramolecular carbanilide cyclization under μW mediation.