Microwave-Mediated Intramolecular Carbanilide Cyclization to Hydantoins Employing Barium Hydroxide Catalysis

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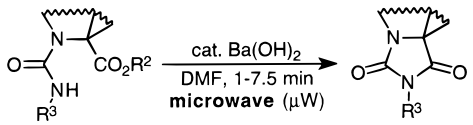
The hydantoin moiety imparts a broad range of biological activities with both medicinal[1] (cf. anticonvulsant) and agrochemical[2] (cf, fungicidal and herbicidal) applications. Given this utility, it is not surprising that a large number of hydantoins adorned with diverse substituents have been synthesized in solution[3] and the solid phase.[4]

In previous studies, we developed novel routes to spiro-fused[5] and polycyclic[6] hydantoin derivatives by carbanilide cyclization chemistry. This strategy delivered hydantoin-containing heterocycles with excellent stereoselective control,[7] but formation of the hydantoin moiety carbanilide cyclization required long reaction times at relatively high temperature with excess base. Indeed, the forcing conditions required for carbanilide cyclization in these studies resulted in some thermal decomposition of product. Following the pioneering work of Giguere and Gedye,[8] microwave (μW) applications in organic chemistry have become more prevalent.[9] The principal advantages of μW mediation are reaction acceleration and accompanying minimization of product decomposition.[9,10]

The current literature reveals a growing number of examples of heterocycle formation mediated by μW irradiation,[11] and our recent report[12] of μW-mediated carbanilide cyclization[13] employing a barium hydroxide catalyst added to this literature. Here, we expand on this previous report and disclose our investigation of numerous carbanilide cyclizations under μW conditions.



1; R^2 = alkyl or polymer **2**

The results of our carbanilide cyclization study are presented in Table 1. Our interest in exploring a μW-mediated route to hydantoins stemmed from our effort in the preparation of spiro[cyclopenta[*d*]isoxazole-4′,5-imidazolidine] heterocycles (**3** → **4**; entries 1 and 2).[5] Here, carbanilide cyclization of **3** required 48 h for complete disappearance of starting material under thermal conditions (2 equiv of Et_3N), and the yield of **4** was modest (62% and 82% for **4a** and **4b**, respectively). Degradation of **3** is the apparent cause of this yield loss.

Prompted by the report by Bose et al.[13] of μW acceleration in cyclizations to nitrogen heterocycles, we submitted carbanilide **3** to Et_3N in DME using a Microwell 10 reactor[14] but were disappointed to find little conversion to **4**.[15] Exploration of a number of base/solvent combinations[16] eventually led us to catalytic barium hydroxide (either anhydrous or octahydrate) in DMF as a nearly ideal medium for μW mediation. Under these conditions, carbanilide **3** delivers spiro-fused hydantoin **4** in nearly quantitative yield (97% and 98% for **4a** and **4b**, respectively) in only 2 min at a μW power setting of 20 W.

We next turned to the conversion of carbanilide **5** to pyrrolo[1,2-*c*]imidazole **6**. Thermal conditions here deliver **6** as the sole product in from 15 to 24 h (Table 1, entries 6−8) in a process that also results in H^d-epimerization to the thermodynamically preferred trans,-anti,trans-stereochemistry. We were surprised to find that mediating carbanilide cyclization of **5** with μW (3 min, 20 W) led to a mixture of two products plus recovered starting material. These two products were obtained in a ∼1:1 ratio in 40+% combined yield and were shown to be H^d-epimers. Thus, while the conventionally heated reaction **5** → **6** proceeds with complete H^d-epimerization, μW-mediation of **5** → **6** (which is also accompanied by reaction heating) can be accomplished with only partial epimerization[9f,17] (Table 1, entries 3−5;

(1) (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (b) Spinks, A.; Waring, W. S. *Prog. Med. Chem.* **1963**, *3*, 313. (c) Karolakwojciechowska, J.; Kwiatkowski, W.; Kieckonono, K. *Pharmazie* **1995**, *50*, 114. (d) Brouillette, Wayne J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S.; DeLorey, T. M.; Brown, G. B. *J. Med. Chem.* **1994**, *37*, 3289. (e) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871.

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(3) Ohta, H.; Jikihara, T.; Wakabayashi, K.; Fujita, T. *Pestic. Biochem. Physiol.* **1980**, *14*, 153.

(4) (a) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909. (b) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603.

(5) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113.

(6) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, in press.

(7) Najdi S.; Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *Tetrahedron Lett.* **1998**, in press.

(8) (a) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. (b) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

(9) For recent reviews, see: (a) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (c) Bram, G.; Galons, H.; Labidalle, S.; Loupy, A. Miocque, M.; Petit, A.; Pigeon, P.; Sansoulet, J. *Bull. Soc. Chim. Fr.* **1989**, 247. (d) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (e) Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, *45*, 567. (f) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233. (g) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18.

(10) Cablewski, T.; Faux, A. F.; Strauss, C. R. *J. Org. Chem.* **1994**, *59*, 3408.

(11) Majetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry*; Kingston, H. M., Haswell, S. J., Eds.; American Chemical Society: Washington, D.C., 1997; pp 455−505.

(12) Gong, Y.-D.; Kurth, M. J. *Tetrahedron Lett.* **1998**, in press.

(13) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 471.

(14) The Micro Well 10 reactor consists of a power head (0−500 W), a time control unit (0−100 min), and a variable power supply (to 600 W).

(15) We examined various bases (Et_3N, DIPEA, DBU) and solvents (benzene, toluene, DMSO, ethanol, diglyme, dimethoxy methane).

(16) We examined various bases (organic bases, see ref 15) and metal bases (NaOH, NaH, *t*-BuOK, LiOH, $BaCO_3$), Lewis acids ($MgCl_2$, $BaCl_2$, LiCl), and solvents (benzene, toluene, DMSO, ethanol, diglyime, dimethoxyethane). We belive catalytic $Ba(OH)_2$ in DMF provides the best conditions for solution-phase intramolecular carbanilide cyclization under mW mediation.

(17) To obtain the maximum quantity of kinetic product **6a**, this reaction was quenched before all the starting material (**5a**) was consumed.

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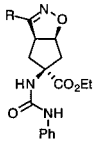
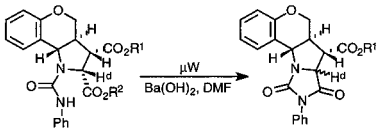
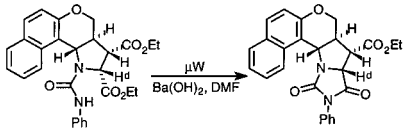
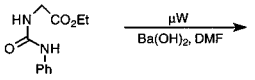
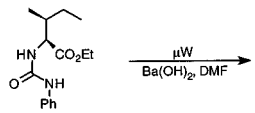
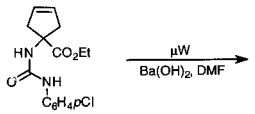
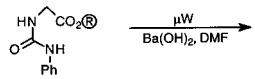
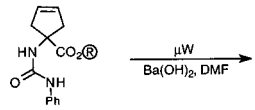
Table 1. Microwave (μW) Intramolecular Carbanilide Cyclization

entry	carbanilide starting material	μW conditions time / power	product & yield (%)	thermal conditions time (h) / yield (%)
1	 **3a**; R = Ph	2 min, 20 W	**4a**; R = Ph (97%)	48 h / 60%[a]
2	**3b**; R = ^{i}Pr	2 min, 20 W	**4b**; R = ^{i}Pr (98%)	48 h / 82%[a]
	 R^1 R^2		H^d = α : β	
3	**5a** Me Et	3 min, 20 W[b]	**6a** 53:47 (44%)[c]	- -
4	**5b** Et Et	3 min, 20 W[b]	**6b** 52:48 (40%)[c]	- -
5	**5c** Et Bn	3 min, 20 W[b]	**6b** 57:43 (58%)[c]	- -
6	**5a** Me Et	7.5 min, 30 W[d]	**6a** 100:0 (91%)	24 h / 82%[e]
7	**5b** Et Et	7.5 min, 30 W[d]	**6b** 100:0 (84%)	24 h / 78%[e]
8	**5c** Et Bn	7.5 min, 30 W[d]	**6b** 100:0 (81%)	15 h / 95%[e]
9	 **7**	2.5 min, 30 W	**8** 0:100 (94%)	8 h / 91%
10	 **9**	4 min, 30 W[f]	**10** (88%)	48 h / 51%
11	 **11**	4 min, 30 W[f]	**12** (90%)	48 h / 54%
12	 **13**	4 min, 20 W[f]	**14** (92%)	48 h / 80%[a]
13	 **15**	12 min, 30 W[g]	**10** (8%)[h]	- -
14	 **16**	10 min, 20 W[i]	**17** (7%)[j]	48 h / 20%[k]

[a] See ref 5. [b] Three 1 min intervals with cooling to 0 °C between intervals. [c] These reactions were quenched before complete conversion of starting material to maximize **6**, and the yield represents the sum yield of both isomers. [d] Three 2.5 min intervals with cooling to room temperature between intervals. [e] See ref 7. [f] Two 2 min intervals with cooling to room temperature between intervals. [g] ® = $(CH_2)_3OCH_2$-polystyrene; six 2 min intervals with cooling to room temperature between intervals. [h] This is a six-step overall yield based on a starting Merrifield resin loading of 2 mequiv/g and is unoptimized. [i] ® = $(CH_2)_3OCH_2$-polystyrene; five 2 min intervals with cooling to room temperature between intervals. [j] This is a five-step overall yield based on a starting Merrifield resin loading of 2 mequiv/g and is unoptimized. [k] This is a five-step overall yield based on a starting Merrifield resin loading of 2 mequiv/g using excess Et_3N in THF for 48 h at reflux.

three 1.0 min μW intervals with cooling to room temperature between intervals). To achieve complete conversion of **5**, we found it most effective to increase the μW power to 30 W and the reaction to 7.5 min (Table 1, entries 6−8; three 2.5 min μW intervals with cooling to room temperature between intervals). These conditions delivered **6** as the sole product (i.e., complete H^d-epimerization) in 81−91% yield.

These μW results with **5** stand in sharp contrast to our observations with naphthyl analogue **7** (Table 1 entry 9). Thermal cyclization of **7** leads only to unepimerized product **8**, which we believe is a consequence of a prohibiting nonbonding interaction that would develop between the hydantoin moiety and the B-ring of the naphthyl moiety upon enamide formation.[6] This same interaction precludes H^d-epimerization in μW reaction **7** → **8**, a transformation that is complete in 2.5 min at 30 W (94% yield).

We investigated the carbanilide cyclization of simple substrate **9** (→ **10**; entry 10) and **11** (→ **12**; entry 11) as well as cyclopentenyl substrate **13** (→ **14**; entry 12). In each of these cases, there was a dramatic reduction in reaction time (Δ requiring 48 h; μW requiring 2 min) and μW-mediation gave dramatically improved yields (Table 1, entries 10 and 11; Δ ~50%, μW ~90%). Unfortunately, Cα-epimerization led to racemization of **12** under both thermal and μW mediation.

Finally, our interest in solid-phase small-molecule chemistry led us to explore μW-mediated carbanilide cyclizations as a method for resin release of hydantoins. Entries 13 and 14 illustrate that μW-mediated solid-phase reaction also enjoys greatly reduced reaction time (**16** → **17** requires 48 h for Δ vs 10 min for μW; see Table 1, entry 14). Further application of this μW advantage will be reported in due course.

In conclusion, μW-mediated intramolecular carbanilide cyclizations occur with significantly reduced reaction time (μW minutes vs Δ hours) for both solution- and solid-phase reactions. Catalytic $Ba(OH)_2$ in DMF is uniquely effective in this μW transformation and, in certain systems, can provide access to unepimerized products not available in thermal transformations.

Experimental Section

General Methods. Microwave heating was carry out with a MicroWell 10 (Labwell, Sweden) monomodal electromagnetic radiation at 2.45 GHz. Analytical TLC was carried out on precoated plates and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh). NMR spectra (^{1}H at 300 MHz; ^{13}C at 75 MHz) were recorded in $CDCl_3$ solvent with chemical shifts expressed in ppm relative to internal TMS. Single-crystal X-ray structure determinations were obtained through the X-ray Crystallography Facility, Department of Chemistry, University of California, Davis.

General Procedure for Intramolecular Carbanilide Cyclization with Catalytic $Ba(OH)_2$ under μW Irradiation (specific for 6a).[7] Carbanilide **5a** (40 mg, 10×10^{-2} mmol) and $Ba(OH)_2 \cdot 8H_2O$ (6 mg, 2×10^{-2} mmol) were mixed together in DMF (1.0 mL) solvent in a Teflon-capped test tube. This vessel was placed in a Micro Well 10 reactor and irradiated for 7.5 min (2.5 min × 3; cooling to room temperature between irradiations) at 30 W. The reaction was quenched with aqueous 10% citric acid water solution (10 mL) and extracted with ethyl acetate (25 mL × 2). The combined organic solution was washed with water (15 mL x 3), dried ($MgSO_4$), and concentrated by rotoevaporation. Purification by flash column chromatography (EtOAc/Hexane/3:7) gave pyrroloimidazole **6a** (34 mg, 8.88×10^{-2} mmol) in 91% yield. All products were characterized by meting point, ^{1}H NMR, ^{13}C NMR, IR, and EA. The structures of **6a** (H^d α),[6] **6b** (H^d β), and **8**[6] were identified by single-crystal

X-ray analysis. Products **4a**,[5] **4b**,[5] **6a**,[6] **6b**,[6] **8**,[6] **10**,[4a] **12**,[4a] **14**,[5] and **17**[5] were described previously.

Acknowledgment. We thank the National Science Foundation and Novartis Crop Protection AG for financial support of this research. We also thank LabWell for providing the Micro Well 10 reactor.

Supporting Information Available: Computer-generated structure from X-ray crystallographic data for compound **6b** (H^d β) (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Additions and Corrections

Vol. 61, 1996

Mark T. Hamman, Clifton S. Otto, Paul J. Scheuer,* and D. Chuck Dunbar. Kahalalides: Bioactive Peptides from a Marine Mollusk *Elysia rufescens* and Its Algal Diet *Bryopsis* sp.

Page 6595. The labeled amino acid on the structure of kahalalide F (**6**) should read D-Pro rather than L-Pro.

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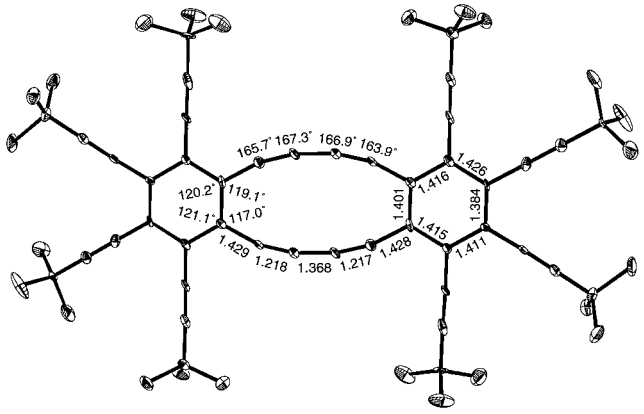
Vol. 62, 1997

John D. Tovar, Norbert Jux, Thibaut Jarrosson, Saeed I. Khan, and Yves Rubin*. Synthesis and X-ray Characterization of an Octaalkynyldibenzooctadehydro[12]-annulene.

Page 3432. In the X-ray characterization of the octaalkynyldibenzooctadehydro[12]annulene, we have recently discovered that a clerical mistake was made in the transfer of X-ray data between computers. The unit cell angle γ was changed in the process from 71.71° to 77.71°. This led to unusual bond elongations in the molecule, which were discussed briefly in the paper as "surprising". As confirmed with the correct data (figure below), the bond lengths and angles are now within normal values and are in accord with the PM3 calculated structure (not shown). We are grateful to Professors François Diederich and Paul von Ragué Schleyer for bringing this error to our attention. For a related discussion of theoretical versus experimental geometries, see: Bühl, M.; Schaefer, H. F., III; Schleyer, P. v. R.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1154−1155. All pages of the Supporting Information have been replaced.



Supporting Information Available: X-ray structure of **3a**·$(CHCl_3)_2$·MeOH; labeled structure and stereoscopic view of the packing structure, tables of atomic coordinates, anisotropic temperature factors, bond lengths, bond angles, and atomic coordinates (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information

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Dennis P. Arnold* and David A. James. Dimers and Model Monomers of Nickel(II) Octaethylporphyrin Substituted by Conjugated Groups Comprising Combinations of Triple Bonds with Double Bonds and Arenes. 1. Synthesis and Electronic Spectra.

Page 3464, column 2, line 28. We stated that the published spectrum for [5,15-bis(trimethylsilylethynyl]-10,20-diphenylporphinato]zinc(II) may be in error. The previously reported spectral data (*Science* **1994**, *264*, 1105−1111) for this compound are in fact correct as originally described.

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Vol. 63, 1998

David E. Hibbs, Michael B. Hursthouse, Iwan G. Jones, Wyn Jones, K. M. Abdul Mallik, and Michael North. Synthesis of Peptides and Pseudopeptides Incorporating an *endo* -(2*S*,3*R*)-Norborn-5-ene Residue as a Turn Inducer.

Page 1496. The authors regret that no reference was made in this manuscript to the impressive work carried out by Nowick and co-workers in the area of β-strand mimics. For a leading reference to this work, see: Nowick, J. S.; Pairish, M.; Lee, I. Q.; Holmes, D. L.; Ziller, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 5413.

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S0022-3263(98)04010-9
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Iwan, G. Jones, Wyn Jones, and Michael North*. Conformational Analysis of Peptides and Pseudopeptides Incorporating an *endo*-(2*S*,3*R*)-Norborn-5-ene Residue as a Turn Inducer.

Page 1504. The authors regret that no reference was made in this manuscript to the impressive work carried out by Nowick and co-workers in the area of β-strand mimics. For a leading reference to this work, see: Nowick, J. S.; Pairish, M.; Lee, I. Q.; Holmes, D. L.; Ziller, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 5413.

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