Microwave Assisted Synthesis of 1,5-Disubstituted Hydantoins and Thiohydantoins in Solvent-Free Conditions

Satya Paul,*[a] Mukta Gupta,[a] Rajive Gupta,[a] André Loupy[b]

[a] Department of Chemistry, University of Jammu, Jammu-180 006, India
Fax +91(191)505086; E-mail: paul7@rediffmail.com

[b] Laboratoire des Réactions Sélectives sur Supports, CNRS UMR 8615, Université Paris-Sud, 91405, Orsay, France
Fax +33(169)154679; E-mail: aloupy@icmo.u-psud.fr

Received 28 June 2001; revised 18 October 2001

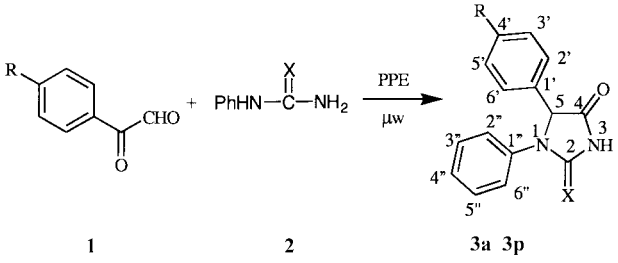
Abstract: 1,5-Disubstituted hydantoins/thiohydantoins **3a**–**p** have been synthesized in 81–95% yield by a microwave-promoted solvent-free condensation of arylglyoxals **1** and phenylurea/thiourea **2** using PPE as a reaction mediator. This method can be extended towards the parallel synthesis of **3**. The workup is simple and involves treatment with ice-cold water.

Key words: arylglyoxals, solvent-free conditions, polyphosphoric ester (PPE), microwave activation, hydantoins

Hydantoins are compounds that have a reactive urea core. They are well known for diverse biological activities and play a key role as antiarrhythmics,[1,2] anticonvulsants,[3,4] antitumor compounds,[5,6] aldose reductase inhibitors,[7] anti-inflammatory compounds,[8] and antiandrogens.[9] They also involved in lowering of blood sugar level in mammals.[10] Hydantoins have also been used for the preparation of moisturizing lotions,[11] for increasing HDL cholesterol concentration,[12] and as antiserotoninergic agents. [13] The most straightforward protocol for the synthesis of 1,5-disubstituted hydantoins **3** involves the one-pot condensation of arylglyoxals **1** with phenylurea **2** in ethanol under strongly acidic conditions (concd HCl and glacial HOAc).[14] However, the combination of solvents, strong acids and long reaction times makes this method environmentally hazardous. Thus, a simple, general and efficient procedure for the synthesis of this important heterocyclic system is required.

The application of microwave irradiation to organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology.[15] The salient features of the microwave approach are rapid reaction rates, cleaner reaction conditions and enhancements in chemical yields.[15]

Under the framework of "Green Chemistry" we have developed an environmentally benign solvent-free approach for the synthesis of hydantoins/thiohydantoins. This allowed the elimination of solvents and strong mineral acids in solution.[16] Further attractions of this method are that it allows reactions in open vessels (thus avoiding the risk of high pressure development) and synthesis on preparative scales.[17] Herein we wish to report a facile microwave synthesis of 1,5-disubstituted hydantoins **3** from arylglyoxals **1** and phenylurea **2** using polyphosphoric ester (PPE) as a reaction mediator. Additionally, this method has been extended to the synthesis of thiohydantoins (by using phenylthiourea instead of phenylurea) under identical reaction conditions.



Scheme

Arylglyoxals were prepared from acetophenones either by using SeO_2/dioxane or SeO_2/SiO_2 under microwave irradiation. In order to carry out the synthesis of 1,5-disubstituted hydantoins/thiohydantoins under efficient environmentally benign conditions, the influence of microwave irradiation on a neat mixture of aryglyoxal **1**, phenylurea/thiourea **2** and PPE was investigated. The molar ratios of reagents, irradiation times, and microwave power levels were optimized to achieve higher yields. Optimum conditions (Table) employed a 1.1:1.0 ratio of aryglyoxal **1** and phenylurea/thiourea **2** with PPE as reaction mediator (2.2 mmoles of **1** required 300mg of PPE).

To demonstrate the feasibility of using microwave irradiation for the parallel synthesis of hydantoins/thiohydantoins four reaction vessels containing the appropriate mixtures of arylglyoxals **1**, phenylurea/thiourea **2** and PPE were simultaneously placed into the oven and irradiated. After workup the individual hydantoins/thiohydantoins were obtained in good to excellent yields.

Finally, the synthesis of **3a** using PPE under neat conditions was attempted using a thermostated oil-bath under identical conditions as those employed as for the microwave-assisted method (3 min and 120 °C). Lower yields were obtained under thermal conditions (36%) as compared to microwave irradiation (88%), demonstrating that

Synthesis 2002, No. 1, 28 12 2001. Article Identifier:
1437-210X,E;2002,0,01,0075,0078,ftx,en;Z07301SS.pdf.

ISSN 0039-7881

Table Microwave/PPE-Mediated Synthesis of **3a**–**p**

Product	R	X	Time (min)	Yield[a] (%)	mp (°C) Found/ Reported
3a	H	O	3	88	192–93/ 195[14]
3b	Me	O	3	92	206–207/ 209–211[19]
3c	OMe	O	2.5	89	176–177
3d	OEt	O	2.5	83	151–152
3e	F	O	2.5	85	193–194/ 185–187[20]
3f	Cl	O	3	81	183–184/ 196–198[19]
3g	Br	O	3	92	205–206/ 204–206[19]
3h	NO_2	O	3	80	143–144
3i	H	S	3	88	232–233
3j	Me	S	3.5	93	242–243
3k	OMe	S	3	83	220–221
3l	OEt	S	3	85	223–224
3m	F	S	2.5	87	223–224
3n	Cl	S	3	95	229–230
3o	Br	S	3	91	206–207
3p	NO_2	S	3.5	95	244–245

[a] Yield of isolated products

the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state.[18] Nucleophilic attack of an amine on a polarized carbonyl function (rate-determining step) is followed by an intramolecular cyclization.

We have developed a novel and efficient microwave-induced method for the synthesis of hydantoins/thiohydantoins. The advantages of this environmentally safe and benign protocol include a simple reaction set-up, high product yields, short reaction times and elimination of solvents and acid. The workup simply involves treatment with ice-cold water. Additionally, we demonstrated that the present procedure is readily amenable to parallel synthesis of hydantoins/thiohydantoins. This rapid and easy technique coupled with solvent-free conditions may contribute to the dream of Green Technology.

Melting points (uncorrected) were determined by a Toshniwal melting point apparatus. IR spectra (ν_{max}) were recorded on Shimadzu435 spectrophotometer using KBr discs. ^{1}H NMR spectra in $CDCl_3$–DMSO-d_6/DMSO-d_6 were recorded on Bruker DRX 300 (300 MHz) and Bruker AM-250 (250 MHz) instruments and ^{13}C NMR in $CDCl_3$–DMSO-d_6/DMSO-d_6 on Jeol FX 90Q (90 MHz) and Bruker DPX-200 (200 MHz) instruments using TMS as an internal standard. Mass spectral data were recorded on a Delsi-Nermag spectral-30 spectrometer. Reactions were carried out in a BPL BMO 800T microwave domestic oven with power output of 800 watts.

Synthesis of arylglyoxals 1 under microwave irradiation; General Procedure.

The appropriate acetophenone (2 mmol) and SeO_2 (3 mmol) were dissolved in CH_2Cl_2 (7 mL). Silica gel (2 g) was added and stirred vigorously. After 5 min, the solvent was removed under vacuum and the dry powder was irradiated in a domestic microwave oven for 7–10 min at 450 W. After the completion of the reaction, the product was extracted with CH_2Cl_2 (3 × 15 mL) and washed with excess of water to remove unreacted SeO_2. The CH_2Cl_2 extract after drying over anhyd Na_2SO_4 and removal under reduced pressure gave aryglyoxal **1** in 68–81% yield.

Microwave/PPEMediated Synthesis of Hydantoins/ Thiohydantoins 3a–p; General Procedure

a) Single-Compound Method

The appropriate arylglyoxal **1** (2.2 mmol), phenylurea/thiourea **2** (2 mmol) and PPE (300 mg) were placed in a beaker (50 mL). After the mixture was mixed thoroughly with the help of a glass rod a paste formed (15–20 s). The beaker was introduced into the microwave oven and irradiated for the appropriate time (Table) at 300 W. Reaction progression was monitored by t.l.c. On cooling to room temperature, crushed ice was added and the mixture was stirred thoroughly (1–2 min), till the solid product was obtained, which was filtered, dried and crystallized from a suitable solvent (benzene–petroleum ether or benzene). The physical data are given in the Table.

b) Parallel synthesis of 3a–e/3i–m

The appropriate arylglyoxal **1** (2.2 mmol), phenylurea/thiourea **2** (2 mmol) and PPE (300 mg) were placed in 4 individual (25 mL) beakers. The mixture in all the 4 beakers was mixed separately until a paste fomed. They were irradiated on the turntable in the microwave oven 5 times at 300 W for 30 s, with 1 min cooling time. After the work up as above, the products were obtained in good to excellent yields (Table). In the case of **3i**–**m**, the irradiation is carried out 6 times at 300 W for 30 s with 1 minute cooling time.

The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and comparison with authentic samples prepared according to the literature methods.[14,19,20]

Spectral data of compounds 3a–p

1,5-Diphenylhydantoin (3a)

IR (Nujol): 3190, 3005, 1750, 1690 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 5.51 (s, 1 H, CH), 7.02–7.52 (m, 10 H, H_{arom}), 11.15 (br. s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR (200 MHz, DMSO-d_6): δ = 171.4 (C2), 154.8 (C4), 136.5 (C11''), 134.0 (C1'), 128.8 (C3'), 128.6 (C3', C5'), 128.4 (C3"), 127.1 (C4'), 124.0 (C4"), 120.7 (C6', C2", C6"), 64.4 (C5).

MS (EI): *m/z* (%) = 252 (31.72) [M$^+$], 253 (100) [M + H$^+$].

5-(4-Methylphenyl)-1-phenylhydantoin (3b)

IR (Nujol): 3200, 2975, 1755, 1690 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 2.31 (s, 3 H, CH_3), 5.47 (s, 1 H, CH), 7.02-7.55 (m, 9 H, H_{arom}), 11.11 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 266 (26.57) [M^+], 267 (100) [M + H^+].

5-(4-Methoxyphenyl)-1-phenylhydantoin (3c)
IR (Nujol): 3195, 2973, 1750, 1690, 1265, 1055 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.89 (s, 3 H, OCH_3), 5.88 (s, 1 H, CH), 6.86–6.89 (d, 2 H, H_{arom}), 7.00–7.05 (t, 1 H, H_{arom}), 7.23–7.28 (m, 4 H, H_{arom}), 7.46–7.48 (d, 2 H, H_{arom}), 11.36 (br. s, 1 H, NH, exchangeable with D_2O).

5-(4-Ethoxyphenyl)-1-phenylhydantoin (3d)
IR (Nujol): 3190, 2975, 1750, 1700, 1250, 1048 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 1.22 (t, 3 H, OCH_2CH_3), 3.8 (q, 2 H, OCH_2CH_3), 5.32 (s, 1 H, CH), 6.61–7.31 (m, 9 H, H_{arom}), 10.75 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 296 (40.06) [M^+].

5-(4-Fluorophenyl)-1-phenylhydantoin (3e)
IR (Nujol): 3200, 2980, 1755, 1695 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 5.47 (s, 1 H, CH), 7.0–7.42 (m, 9 H, H_{arom}), 10.92 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 270 (71.58) [M^+], 271 (100) [M + H^+].

5-(4-Chlorophenyl)-1-phenylhydantoin (3f)
IR (Nujol): 3150, 2975, 1760, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 5.25 (s, 1 H, CH), 7.23–7.44 (m, 9 H, H_{arom}), 11.22 (br. s, 1 H, NH, exchangeable with D_2O).

5-(4-Bromophenyl)-1-phenylhydantoin (3g)
IR (Nujol): 3155, 2975, 1755, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 5.31 (s, 1 H, CH), 7.25–7.60 (m, 9 H, H_{arom}), 11.12 (br. s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR (200 MHz, DMSO-d_6): δ = 171.4 (C2), 154.8 (C4), 136.3 (C1”), 133.2 (C5’), 131.7 (C3’), 129.1 (C2’, C6’), 128.6 (C3”, C5”), 124.1 (C4’, C4”), 121.9 (C1’), 120.6 (C2”, C6”), 63.7 (C5).

5-(4-Nitrophenyl)-1-phenylhydantoin (3h)
IR (Nujol): 3160, 2975, 1755, 1695 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.20 (s, 1 H, CH), 7.02–7.07 (t, 1 H, H_{arom}), 7.25–7.30 (t, 2 H, H_{arom}), 7.47–7.49 (d, 2 H, H_{arom}), 7.65–7.68 (d, 2 H, H_{arom}), 8.16–8.20 (d, 2 H, H_{arom}), 11.55 (br. s, 1 H, NH, exchangeable with D_2O).

1,5-Diphenylhiohydantoin (3i)
IR (Nujol): 3195, 2995, 1748, 1182 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 5.59 (s, 1 H, CH), 7.31-7.50 (m, 10 H, H_{arom}), 11.00 (br. s, 1 H, NH, exchangeable with D_2O).

5-(4-Methylphenyl)-1-phenylthiohydantoin (3j)
IR (Nujol): 3175, 2980, 1750, 1178 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 2.39 (s, 3 H, CH_3), 5.25 (s, 1 H, CH), 7.23–7.60 (m, 9 H, H_{arom}), 10.74 (br. s, 1 H, NH, exchangeable with D_2O).

5-(4-Methoxyphenyl)-1-phenylthiohydantoin (3k)
IR (Nujol): 3200, 2975, 1740, 1250, 1162, 1052 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 3.88 (s, 3 H, OCH_3), 5.27 (s, 1 H, CH), 6.95–7.58 (m, 9 H, H_{arom}), 10.95 (br. s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR (90 MHz, $CDCl_3$–DMSO-d_6): δ = 183.3 (C4), 172.9 (C2), 160.1 (C4’), 128.3 (C1’), 125.6 (C2’, C3”, C5”), 125.2 (C6’), 123.4 (C1”), 112.3 (C3’, C5’, C 2”, C4”, C6”), 61.9 (C5), 55.5 (OCH_3).

MS (EI): *m/z* (%) = 298 (31.12) [M^+], 299 (100) [M + H^+].

5-(4-Ethoxyphenyl)-1-phenylthiohydantoin (3l)
IR (Nujol): 3163, 2979, 1754, 1246, 1186, 1044 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 1.40 (t, 3 H, OCH_2CH_3), 4.05 (q, 2 H, OCH_2CH_3), 5.25 (s, 1 H, CH), 6.87–7.49 (m, 9 H, H_{arom}), 10.78 (br. s, 1 H, NH, exchangeable with D_2O).

^{13}C NMR (90 MHz, DMSO-d_6): δ = 182.3 (C4), 172.2 (C2), 160.0 (C4’), 127.5 (C1’), 124.2 (C2’, C3”, C5”), 123.1 (C6’), 122.4 (C1”), 112.0 (C3’, C5’, C2”, C4”, C6”), 62.1 (C5), 61.1 (OCH_2CH_3), 13.81 (OCH_2CH_3).

MS (EI): *m/z* (%) = 312 (100) [M^+].

5-(4-Fluorophenyl)-1-phenylthiohydantoin (3m)
IR (Nujol): 3188, 2995, 1770, 1185 cm^1.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 5.25 (s, 1 H, CH), 7.08–7.51 (m, 9 H, H_{arom}), 10.66 (br. s, 1 H, NH, exchangeable with D_2O).

5-(4-Chlorophenyl)-1-phenylthiohydantoin (3n)
IR (Nujol): 3150, 3005, 1800, 1182 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 5.30 (s, 1 H, CH), 7.25–7.55 (m, 9 H, H_{arom}), 10.75 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 302 (36.75) [M^+], 303 (100) [M + H^+].

5-(4-Bromophenyl)-1-phenylthiohydantoin (3o)
IR (Nujol): 3158, 2971, 1758, 1195 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$–DMSO-d_6): δ = 5.22 (s, 1 H, CH), 7.17–7.65 (m, 9 H, H_{arom}), 11.11 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 347 (100) [M^+].

5-(4-Nitrophenyl)-1-phenylthiohydantoin (3p)
IR (Nujol): 3152, 2975, 1735, 1177 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 5.52 (s, 1 H, CH), 7.20–8.35 (m, 9 H, H_{arom}), 11.10 (br. s, 1 H, NH, exchangeable with D_2O).

MS (EI): *m/z* (%) = 313 (42.62) [M^+], 314 (100) [M + H^+].

Acknowledgement

Financial support from UGC, New Delhi and JRF to MG is gratefully acknowledged. We thank RSIC, CDRI Lucknow for recording NMR and mass spectral data.

References

(1) Havera, H. J.; Stryeker, W. G. US Patent 3835151, **1973**; *Chem. Abstr*. **1974**, *81*, 152224m.
(2) Havera, H. J.; Stryeker, W. G. US Patent 3994904, **1976**; *Chem. Abstr*. **1977**, *86*, 106586m.
(3) El-Kerdawy, M. M.; Tantawy, A. S.; Abououf, A. A. *Egypt. J. Chem.* **1974**, *17*, 845.
(4) Dziedzic, B.; Szadowska, A.; Kaminska, A. *Acta Pol. Pharm.* **1978**, *35*, 423.
(5) Rodgers, T. R.; Lamontagne, M. P.; Markovc, A.; Ash, A. B. *J. Med. Chem.* **1977**, *20*, 591.
(6) Valavicient, J.; Blyum, R. A.; Lutsenko, V. V. *Poliskilzuch, Portivoopukholevykh, Protivovospalitelmykh Mutagennykh Veshchestv* **1977**, 44; *Chem. Abstr*. **1978**, *88*, 105221t.

(7) Sarges, R.; Sehnur, R. US Patent 4127665, **1978**; *Chem. Abstr*. **1979**, *90*, 87464j.
(8) Schulte, K. E.; Von, W. V. *Eur. J. Med. Chem.-Chim. Ther*. **1978**, *13*, 25.
(9) Claussuer, A.; Goubet, F.; Teutsch, J.-J. PCT Int. Appl. WO 97 19064, **1997**; *Chem. Abstr*. **1997**, *127*, 50640v.
(10) Hussain, I.; Nasir, M. *J. Ind. Chem. Soc.* **1979**, *56*, 177.
(11) Seki, T. Jpn. Kokai Tokkyo Koho JP 09278645, **1997**; *Chem. Abstr*. **1997**, *127*, 362483q.
(12) Elokdah, H. M.; Chai, S.-Y.; Sulkowski, T. S.; Strike, D. P. PCT Int. Appl. WO 97 19932, **1997**; *Chem. Abstr*. **1997**, *127*, 81453r.
(13) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dudsworth, S.; Sang, P. Y.; Knigh, C.; Williams, M.; Maxwell, M.; Glen, R. C. *J. Med. Chem.* **1999**, *42*, 2504.
(14) Joshi, K. C.; Pathak, V. N.; Goyal, M. K. *J. Heterocycl. Chem.* **1981**, *18*, 1651.
(15) For recent reviews on microwave-assisted organic reactions: (a) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851. (b) Varma, S. *Green Chemistry* **1999**, *1*, 43. (c) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213. (d) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18. (e) Majetich, G.; Hicks, R. *J. Microwave Power* **1995**, *30*, 27. (f) Abramovitch, R. A. *Org. Prep. Proced. Int.* **1991**, *2*, 683.
(16) Loupy, A. *Topics of Current Chemistry: Modern Solvents in Organic Synthesis*, Vol. 206; Knochel, P., Ed.; Springer Verlag: New York, **1999**, 153.
(17) Cleophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev*. **2000**, *6*, 498.
(18) (a) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161. (b) Perreux, L.; Loupy, A. *Tetrahedron*, in press.
(19) Arnold, K.; Moebius, G. Ger. Patent (East) 89846DD, **1972**; *Chem. Abstr*., **1972**, *77*, 126634.
(20) Pentassuglia, G.; Araldi, G. L.; Donati, D.; Feriani, A.; Oliosi, B.; Pasquarello, A.; Ursini, A. *Farmaco* **1997**, *52*, 573.