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Facile Synthesis of Hydantoin Derivatives under Microwave Irradiation

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The rapid and highly efficient synthesis of hydantoin derivatives **3(a-f**) was achieved under microwave irradiation by using a domestic microwave oven from the reactions of cyanohydrin derivatives **2(a-f)** with ammonium carbonate. The reaction proceeded rapidly (2-5 min.), and as a result a series of hydantoin derivatives **3(a-f**) were obtained in high yields. All of the synthesized compounds were fully characterized by their melting point, ^{1}H-NMR, FTIR spectroscopy and elemental analyses. Cyanohydrin derivatives **2(a-f**) were also prepared from the ketone derivatives **1(a-f**) with potassium cyanide in the presence of sodium metabisulfite in an additional reaction.

Introduction

In recent years, microwave irradiation using commercial domestic ovens for the optimization and acceleration of organic reactions has rapidly increased[1−2].It has been reported that a variety of reactions such as Diels-alder [3], ene[4], Claisen reactions[5], Fischer cyclization[6], synthesis of heterocycles[7], hydrolysis of esters[8], hydrogenation[9], deprotection of benzyl ester[10], deacetylation of diacetates[11], oxazoline formation[12] and polymer synthesis[13−17] could be facilitated by microwave irradiation in a good energy transferring medium.

Over the last few decades, there has been considerable interest in the synthesis and characterization of hydantoin derivatives as an important class of heterocyclic compounds. Hydantoin derivatives that display interesting activities against a broad range of biological targets have been identified[18]. These compounds are used as anticonvulsants in the treatment of epilepsy and heart arrhythmia. In the chemical industry various 5,5-disubstituted hydantoins constitute the basis of a new generation of weatherproof high-temperature-stable epoxy resins[19]. Furthermore, hydantoin and hydantoin derivatives were used as a monomer for the synthesis of condensation polymers. Recently, we have synthesized a series of new optically active poly(amide-imide)s prepared by the polycondensation reactions of 4,4'-carbonyl-bis(phthaloyl-L−alanine) diacid chloride with 6 different derivatives of hydantoin and thiohydantoin compounds using a domestic microwave oven[20−21]. We report in this paper a facile method for the synthesis of some hydantoin derivatives under microwave irradiation.

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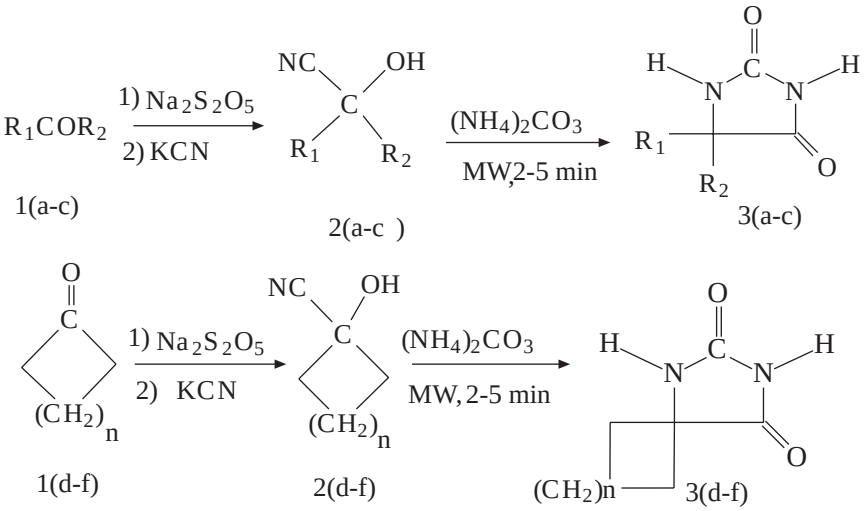


	3a	3b	3c
R_1	CH_3	CH_3	C_2H_5
R_2	CH_3	C_2H_5	C_2H_5

	3d	3e	3f
n	2	3	4

Scheme

Experimental

All chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) and Merck Chemical Co. (Germany). Melting points were determined using an electrothermal digital melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 500 MHz instrument. Fourier transform infrared (FTIR) spectra were recorded on a Galaxy series FTIR 5000 spectrophotometer (England). Spectra of solids were performed using KBr pellets. Vibrational transition frequencies were reported in wave number (cm^{-1}). Band intensities were assigned as weak (w), medium (m), shoulder (sh), strong (s) and broad (br). Elemental analyses were performed by the Research Institute of Petroleum Industry, Tehran, Iran. As a source of microwave irradiation, we used a Samsung domestic microwave oven (2450 MHz, 900 W) to carry out the reactions.

Preparation of cyanohydrin derivatives 2(a-f)

All of the cyanohydrin derivatives **2(a-f)** were synthesized by a typical procedure that is shown in scheme. Eleven grams of sodium metabisulfite was dissolved into 20 mL of cold water and placed in a 100 mL round-bottomed flask. Then ketone **1(a-f)** (0.1 mol) was added slowly whilst swirling the liquid mixture steadily. This was followed by the addition of 6 g of potassium cyanide dissolved in 20 mL of cold water. During this slow addition, the cyanohydrin derivatives were separated out as the upper layer. When the separation was completed, the contents of the flask were transferred to a separating funnel and the lower layer was removed. The upper layer was transferred to a flask, and sodium sulfate was then added to dry the product. The dried cyanohydrin derivatives were slightly discolored.

Preparation of hydantoin derivative 3(a-f)

The same method was used for the synthesis of the hydantoin derivative **3(a-f)** shown in the Scheme. The cyanohydrin derivatives **2(a-f)** (0.025 mole) and the freshly powdered ammonium carbonate (4.80 g, 0.05 mole) were placed in a reaction vessel and the mixture was ground until a fine powder was obtained. Then the reaction mixture was irradiated in the microwave oven at full power for 2-5 min. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the reaction mixture was poured into 25 mL of water. After the usual workup, the hydantoin derivatives **3(a-f)** were recrystallized from proper solvent. In Table 1 the observed melting points, % yields, irradiation time, recrystallization solvents, formula and elemental analysis of the final products are listed.

Table 1. Yields, melting points, irradiation time, recrystallization solvents, formula and elemental analysis for hydantoins **3 (a-f)**.

Compd.	mp (°C)	Recrystal Solvent	Irradiation time (min)	Yield	Found (required) (%)			
					Formula	C	H	N
3a	177-178	H_2O	2	75	$C_5H_8N_2O_2$	47.0 (46.87)	6.3 (6.25)	21.5 (21.87)
3b	128-130	EtOH-H_2O (1:1)	3.5	71	$C_6H_{10}N_2O_2$	50.9 (50.70)	7.2 (7.04)	19.5 (19.71)
3c	171-174	EtOH-H_2O (1:1)	4	68	$C_7H_{12}N_2O_2$	54.2 (53.84)	7.9 (7.69)	17.6 (17.94)
3d	190-192	EtOH	3.5	75	$C_7H_{10}N_2O_2$	55.1 (54.54)	6.7 (6.49)	17.8 (18.18)
3e	209-211	EtOH	3	80	$C_8H_{12}N_2O_2$	57.5 (57.14)	7.3 (7.14)	16.0 (16.66)
3f	198-199	EtOH	4.5	62	$C_9H_{14}N_2O_2$	60.0 (59.34)	7.9 (7.69)	14.8 (15.38)

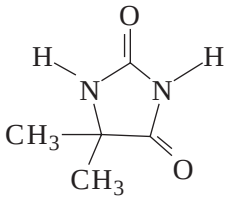
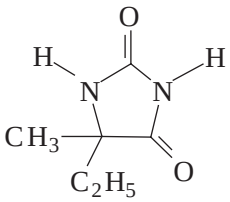
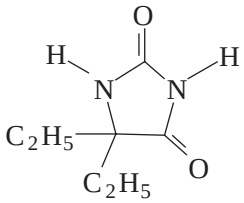
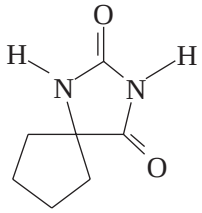
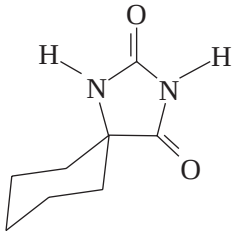
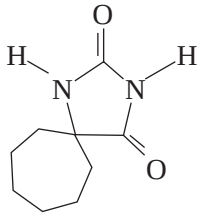
Results and Discussion

In the present work 6 different derivatives of hydantoins such as 5,5-dimethyl hydantoin (**3a**), 5-ethyl-5-methyl hydantoin (**3b**), 5,5-diethyl hydantoin (**3c**), 5-spirocyclopentyl hydantoin (**3d**), 5-spirocyclohexyl hydantoin (**3e**) and 5-spirocycloheptyl hydantoin (**3f**) were prepared in good yields through the Bucherer-Berg synthesis under microwave irradiation using a domestic microwave oven. All of the products were obtained in good yields. Their yields varied from 60 to 80% depending on the nature of the R_1 and R_2 groups. The optimum period of reaction time (irradiation time) was found to be 2-5 min; shorter irradiation times provided a low yield of hydantoin derivatives while longer irradiation times caused degradation. From the results summarized in Table 1 the generality of the reaction is evident as a variety of cyanohydrin derivatives **2(a-f)** react to form hydantoin derivatives **3(a-f)** in good yields within a very short period of irradiation. The reactions are fairly clean and are free from common byproducts.

Table 2. Obtained yields using solution and microwave methods.

Methods	Hydantoins					
	3a	**3b**	**3c**	**3d**	3e	**3f**
Solution	45	32	35	48	50	30
Microwave	75	71	68	75	80	62

Table 3. ^{1}H-NMR and FTIR Spectral Data of Hydantoins **3 (a-f)**.

Compd. **(Formula)**	Structure	Spectral Deta
3a **($C_5H_8N_2O_2$)**		^{1}H-NMR (500 MHz, DMSO-d_6): 1.20-1.25 (s, 6H), 7.90(s, br, 1H), 9.10 (s, br1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 24.62**,** 58.86, 155.96, 179.16 ppm. **FTIR(KBr):** 3240 (s), 3195 (s), 1770 (s), 1747 (s), 1718 (s, br), 1440 (s), 1429 (s), 1381 (s), 1213 (s), 1148 (s), 1053 (s), 925 (s), 798 (m), 769 (s), 650 (s), 600 (m), 449 (s) cm^{-1}
3b **($C_6H_{10}N_2O_2$)**		^{1}H-NMR(500 MHz, DMSO-d_6): 0.70-0.80 (t, 3H, 7 Hz), 1.20-1.25 (s, 3H), 1.40 -1.50 (m, 1H), 1.60-1.65 (m, 1H), 7.80-7.90 (s, br, 1H), 10.50 (s, br, 1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 7.69, 19.40, 22.95**,** 62.11, 154.15, 179.59 ppm. **FTIR(KBr):** 3244 (s), 3053 (s), 1770 (s), 1747 (s), 1718 (s, br), 1440 (s), 1429 (s), 1381 (s), 1213 (s), 1148 (s), 1053 (s), 925 (s), 798 (m), 769 (s), 650 (s), 600 (m), 449 (s) cm^{-1}
3c **($C_7H_{12}N_2O_2$)**		^{1}H-NMR(500 MHz, DMSO-d_6): 0.70-0.80 (t, 6H, 7 Hz), 1.50-1.55 (m, 2H), 1.60-1.65 (m, 2H), 7.70-7.80 (s, br, 1H), 10.50 (s, br, 1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 8.02, 24.51**,** 68.75, 157.39, 175.19 ppm. **FTIR (KBr):** 3240 (s), 3192 (s), 3072 (m), 1739 (s), 1710 (s), 1718 (s, br), 1406 (s), 1381 (s), 1325 (s), 1238 (s), 1157 (m), 1012(s), 925 (s), 792 (s), 756 (s) cm^{-1}
3d **($C_7H_{10}N_2O_2$)**		^{1}H-NMR(500 MHz, DMSO-d_6): 1.60-1.80 (m, 4H), 2.00-2.20 (m, 4H), 7.90 (s, br, 1H), 8.50 (s, br, 1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 22.31, 34.84, 70.23**,** 157.44, 176.50 ppm. **FTIR (KBr):** 3244 (s), 3184 (s), 3078 (m), 1776 (s, br), 1732 (s, br), 1415 (s), 1313 (w), 1074 (m), 790 (w), 750 (m), 717 (m), 644 (m) cm^{-1}
3e **($C_8H_{12}N_2O_2$)**		^{1}H-NMR(500 MHz, DMSO-d_6): 1.22-1.27 (m, 2H), 1.47-1.62 (m, 8H), 6.23 (s, br, 1H), 8.37 (s, br, 1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 21.71, 25.33, 39.76**,** 62.89, 157.51, 179.61 ppm. **FTIR (KBr):** 3244 (s), 3195 (s), 3070 (m), 2939 (s), 1776 (s), 1737 (s), 1458 (m), 1381(s), 1325 (s), 1230 (s), 1072 (m), 925 (w), 778 (m), 756(s) cm^{-1}
3f **($C_9H_{14}N_2O_2$)**		^{1}H-NMR(500 MHz, DMSO-d_6): 1.50-1.90 (m, 12H), 8.21 (s, br, 1H), 9.84 (s, br, 1H) ppm. **^{13}C-NMR (500 MHz, DMSO-d_6):** 21.80, 25.04, 35.20**,** 65.10, 156.15, 173.22 ppm. **FTIR (KBr):** 3292 (s), 3209 (s), 2941 (m), 1770 (s), 1710 (s), 1402 (s), 381 (m), 1218 (w), 1157 (w), 1012 (w), 765 (m), 642 (m) cm^{-1}

The yields of the resulting hydantoins **3(a-f)** obtained by microwave-assisted reaction were compared with those obtained by conventional thermal reaction[22] and are shown in Table 2. These data indicate that the internal heat generation of the reaction mixture under microwave irradiation was much more effective for the progress of the reaction over a shorter reaction time.

The FTIR spectra of hydantoin derivatives **3(a-f)** showed 2 strong peaks between 3200 and 3400 cm^{-1} that were assigned to the N-H of the imide and amide groups. Absorption bands between 1780 and 1700 cm^{-1} which were characteristic peaks for 2 asymmetric and symmetric stretching of the carbonyl groups.

The ^{1}H-NMR spectra of hydantoin derivatives **3(a-f)** showed 2 broad peaks between 8 and 11 ppm that were assigned to the N-H of the imide and amide groups. Table 3 shows the ^{1}H-NMR and FTIR spectral data of hydantoin derivatives **3(a-f).**

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