Ultrasound-enhanced Green Synthesis of 5,5-Diphenylhydantoin Derivatives Using Symmetrical or Unsymmetrical Benzils

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A rapid, highly efficient and mild green synthesis of 5,5-diphenylhydantoin derivatives was achieved from the reaction of symmetrical or unsymmetrical benzil derivatives with urea in the presence of ethanolic KOH under ultrasound irradiation. This simple method affords 5,5-diphenylhydantoin derivatives at room temperature in short reaction time with high yield and purity. This study aimed to overcome the limitations and drawbacks of the reported methods such as tedious work-up, low yield and long reaction time.

Keywords 5,5-diphenylhydantoin, benzil, ultrasound, green synthesis

Introduction

The imidazolidine-2,4-dione, or hydantoin nucleus, is a common 5-membered ring containing a reactive cyclic urea core. Hydantoins are important anticonvulsant drugs.[1,2] Also, they have a number of other biological activities as antiarrhythmic[3,4] and antitumor drugs,[5] bactericides and fungicides.[6] In recent years, considerable efforts have been devoted to the development of novel and more efficient methods for the preparation of hydantoin derivatives. Besides conventional multi-step methods, one-pot,[7] solid-phase[8] and microwave-assisted[9-11] approaches have been published. Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions.[12,13] UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of pure products in high yields, easy manipulation and considered processing aid in terms of energy conservation and waste minimization compared with traditional methods and this technique is more convenient to take green chemistry concepts into accounts.[14-16] In this work, we wish to report a rapid and efficient synthesis of 5,5-diphenylhydantoins using ultrasound irradiation.

Experimental

Materials and instruments

In a typical procedure chemicals were purchased from Merck chemical company. ^{1}H NMR (500 MHz, 60 MHz), and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DPX-500 Avance spectrometer. Tetramethyl silane (TMS) was used as an internal reference. IR spectra were obtained on a Magna-550 Nicolet instrument. Vibrational transition frequencies were reported as wave numbers (cm^{-1}), and band intensities designated as week (w), medium (m) and strong (s). A mass spectrum was recorded by a QP-1100EX Shimadzu spectrometer. Sonication was performed in a UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 24 kHz and the output power was 0—400 W through manual adjustment. UV spectra were recorded on a Hitachi 200—20 spectrometer using spectrophotometric grade ethanol (Baker). Melting points were obtained with a micro melting point apparatus (Electrothermal, Mk3) and are uncorrected.

General procedure for the synthesis of 2a—2j

Classical method To a solution of 10 mmol of benzil or benzil derivatives and 18.7 mmol of urea in 25 mL of ethanol, 16 mL of 1.2 mol•L^{-1} aqueous KOH was added under reflux conditions (temperature: 110—120 ℃). The completion of reaction was monitored by TLC [*V*(petroleum ether)∶*V*(ethyl acetate)= 5∶5]. The reaction mixture was cooled before adding 30 mL of cold water. Then the clear solution was cautiously acidified with concentrated hydrochloric acid and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol.

Ultrasonic irradiation To a solution of 2 mmol of

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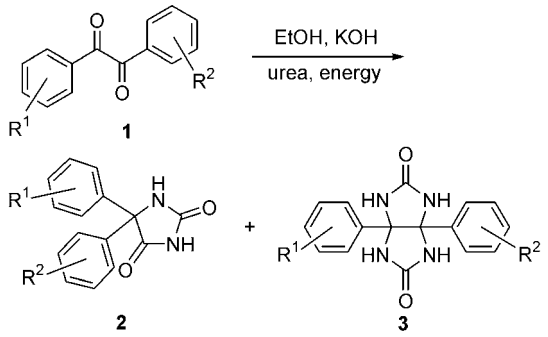
Received September 2, 2009; revised October 12, 2009; accepted November 16, 2009.

benzil or benzil derivatives and 3.7 mmol of urea in 5 mL of ethanol, 3.2 mL of 1.2 mol•L^{-1} aqueous KOH was added and the reaction mixture was exposed to ultrasonic irradiation at room temperature. The completion of reaction was monitored by TLC [*V*(petroleum ether)∶*V*(ethyl acetate)=5∶5]. The reaction mixture was cooled before adding 15 mL of cold water. Then the clear solution was cautiously acidified with concentrated hydrochloric acid and the product was collected by vacuum filtration and washed thoroughly with water. The product was recrystallized from ethanol. The structures of these compounds have been investigated using different methods of spectrometry: IR, ^{1}H NMR, ^{13}C NMR, MS and UV.

Results and discussion

The most straightforward condition for the synthesis of 5,5-diphenylhydantoin is the base-catalyzed condensation using benzil and urea, known as Biltz synthesis.[17] Dunnavant and James showed that the reaction proceeded via a benzilic rearrangement. The formation of 5,5-diphenylhydantoin involves a molecular rearrangement in which a phenyl group undergoes a 1,2-shift.[18] In this work, several 5,5-diphenylhydantoin derivatives were synthesized from the reaction of symmetrical or unsymmetrical benzil derivatives with urea in ethanolic KOH (Scheme 1).

Scheme 1 Synthetic route to 5,5-diphenylhydantoin from urea and benzil derivatives in ethanolic KOH under reflux conditions (temperature: 110—120 ℃) and ultrasound irradiation at room temperature



For examination of the influence of ultrasound irradiation in this reaction, the synthesis of 5,5-diphenylhydantoin was investigated under two procedures, the classical one under thermal heating and an ultrasonic irradiation approach (Table 1). As illustrated in Table 1, method B is better in both yields and especially in the reaction time than method A. On the other side, the principal limitation of Biltz synthesis is the concomitant formation of **2** and **3**. Under ultrasound irradiation, the high yield transformations were carried out without any significant amounts of undesirable side product **3**. From the results in Table 1, it seemed that the benzils containing electron-withdrawing groups were found to be more reactive and could react with urea rapidly (**1f**, **1g**). In contrast, the benzils containing electron-donating groups have shown lower reactivity (**1j**, **1k**, **1c**). These results show that the electronic effects of benzil substituents have a significant role in the rate of this reaction. In total, the results illustrated the high ability of this method for the synthesis of 5,5-diphenyl-hydantoin derivatives.

Spectroscopic data

5,5-Diphenylhydantoin (2a) UV (CH_3OH) λ_{max}: 238 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 7.35—7.41 (m, 10H), 9.17 (s, NH), 10.92 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 73.35 (C), 125.26 (4CH), 127.53 (2CH), 129.88 (4CH), 133.63 (2C), 158.41 (CO), 175.13 (CO); IR (KBr) *v*: 3020, 3340 (s, NH), 1650, 1740 (C=O, s), 1440—1510 (m, C=C), 700 (m, CH) cm^{-1}; MS (70 eV) *m*/*z*: 252 (M^+), 223, 209, 180, 104, 77.

5,5-Bis(4-methylphenyl)hydantoin (2b) UV (CH_3-OH) λ_{max}: 235 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 2.42 (s, 6H), 6.78—6.89 (m, 8H), 8.96 (s, NH), 10.78 (s,

Table 1 Synthesis of 5,5-diphenylhydantoin derivatives in ethanol under reflux conditions (method A) and ultrasound irradiation at room temperature (method B)

Entry	R^1	R^2	Method A		Method B		m.p.$_{rep}$ [a]/℃	m.p.$_{lit.}$ [b]/℃
			Time/min	Yield/%	Time/min	Yield/%		
a	H	H	30	82	3	98	295—297	295—299[c]
b	4-CH_3	4-CH_3	45	74	5	98	296—298	295—299[c]
c	3-CH_3	3-CH_3	56	78	6	96	316—318	—
d	4-Cl	4-Cl	51	79	5	95	218—220	222—227[c]
f	3-NO_2	3-NO_2	16	85	2	96	273—275	—
g	2-NO_2	2-NO_2	13	80	2	94	234—236	230—234[c]
h	4-CH_3	H	37	77	4	97	223—225	—
i	4-OCH_3	H	48	69	5	96	225—227	222[d]
j	4-$N(CH_3)_2$	H	55	63	6	94	226—228	229[d]
k	4-OCH_3	3-Br	52	67	6	98	203—205	—

[a] Reported melting points; [b] Literatured melting points; [c] Reference 11; [d] Reference 19.

NH); ^{13}C NMR (DMSO, 125 MHz) δ: 24.15 ($2CH_3$), 75.27 (C), 128.10 (2C), 128.98 (4CH), 130.87 (4CH), 135.22 (2C), 157.23 (CO), 174.31 (CO); IR (KBr) v: 3020, 3360 (s, NH), 1650, 1800 (s, C=O), 1400—1520 (m, C=C), 760 (m, CH) cm^{-1}; MS (70 eV) m/z: 280 (M^+), 251, 237, 208, 180, 118, 104, 91, 77.

5,5-Bis(3-methylphenyl)hydantoin (2c) UV (CH_3OH) λ_{max}: 236 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 3.6 (s, 6H), 6.80—7.22 (m, 8H), 9.20 (s, NH), 11.00 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 22.43 ($2CH_3$), 78.17 (C), 124.56 (2CH), 127.35 (2CH), 128.14 (2CH), 129.06 (2CH), 134.39 (2C), 137.73 (2C), 156.48 (CO), 174.22 (CO); IR (KBr) v: 3020, 3340 (s, NH), 1650, 1760 (s, C=O), 1460—1520 (m, C=C), 780 (m, CH) cm^{-1}; MS (70 eV) m/z: 280 (M^+), 251, 237, 208, 180, 118, 104, 91, 77.

5,5-Bis(4-chlorophenyl)hydantoin (2d) UV (CH_3OH) λ_{max}: 234 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 7.12—7.24 (m, 8H), 9.40 (s, NH), 11.12 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 77.29 (C), 125.86 (4CH), 127.34 (2C), 129.68 (4CH), 132.55 (2C), 155.96 (C), 174.09 (C); IR (KBr) v: 3000, 3300 (s, NH), 1670, 1790 (s, C=O), 1400—1500 (m, C=C), 770 (m, CH) cm^{-1}; MS (70 eV) m/z: 320 (M^+), 291, 277, 248, 215, 180, 138, 111, 104, 77.

5,5-Bis(3-nitrophenyl)hydantoin (2e) UV (CH_3OH) λ_{max}: 242 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 7.40—8.51 (m, 8H), 8.90 (s, NH), 11.85 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 75.68 (C), 119.17 (2CH), 124.87 (2CH), 130.46 (2CH), 131.79 (2C), 131.96 (2CH), 150.15 (2C), 156.90 (CO), 176.23 (CO); IR (KBr) v: 2900, 3500 (s, NH), 1660, 1750 (s, C=O), 1520—1550 (m, C=C), 1430, 1500 (s, N=O), 760 (m, CH) cm^{-1}; MS (70 eV) m/z: 342 (M^+), 313, 299, 270, 225, 180, 149, 122, 104, 77.

5,5-Bis(2-nitrophenyl)hydantoin (2f) UV (CH_3OH) λ_{max}: 240 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 7.52—8.10 (m, 8H), 9.20 (s, NH), 11.70 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 76.85 (C), 123.01 (2CH), 123.58 (2CH), 127.65 (2CH), 131.52 (2CH), 131.69 (2C), 150.07 (2C), 156.49 (CO), 173.72 (CO); IR (KBr) v: 3000, 3200 (s, NH), 1650, 1700 (s, C=O), 1490—1520 (m, C=C), 1400—1450 (s, N=O), 770 (m, CH) cm^{-1}; MS (70 eV) m/z: 342 (M^+), 313, 299, 270, 180, 149, 122, 104, 77.

5-(4-Methylphenyl)-5-phenylhydantoin (2g) UV (CH_3OH) λ_{max}: 232 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 2.58 (s, 3H), 7.00—7.40 (m, 9H), 9.40 (s, NH), 10.84 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 25.07 (CH_3), 76.98 (C), 126.45 (C), 127.37 (2CH), 127.86 (2CH), 128.09 (CH), 128.62 (2CH), 129.84 (2CH), 131.20 (C), 136.96 (C), 153.94 (C), 175.77 (C); IR (KBr) v: 3020, 3300 (s, NH), 1660, 1750 (s, C=O), 1400—1460 (m, C=C), 760 (m, CH) cm^{-1}; MS (70 eV) m/z: 266 (M^+), 237, 223, 194, 180, 118, 104, 91, 77.

5-(4-Methoxyphenyl)-5-phenylhydantoin (2h) UV (CH_3OH) λ_{max}: 234 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 3.73 (s, 3H), 6.94—7.40 (m, 9H), 9.21 (s, NH), 11.02 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 55.61 (CH_3), 73.23 (C), 114.19 (2CH), 127.14 (2CH), 127.30 (2CH), 128.86 (2CH), 128.92 (CH), 132.33 (C), 140.36 (C), 156.38 (C), 159.31 (C), 175.52 (C); IR (KBr) v: 3000, 3400 (s, NH), 1670, 1810 (s, C=O), 1380—1520 (m, C=C), 700 (m, CH) cm^{-1}; MS (70 eV) m/z: 282 (M^+), 253, 239, 210, 180, 134, 107, 104, 77.

5-(4-Dimethylaminophenyl)-5-phenylhydantoin (2i) UV (CH_3OH) λ_{max}: 235 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 3.51 (s, 6H), 6.74—7.47 (m, 9H), 9.00 (s, NH), 10.78 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 43.26 ($2CH_3$), 77.63 (C), 112.48 (2CH), 113.72 (C), 127.46 (2CH), 127.79 (2CH), 128.04 (CH), 128.59 (2CH), 135.61 (C), 140.31 (C), 151.22 (C), 156.47 (C), 175.81 (C); IR (KBr) v: 3120, 3340 (s, NH), 1650, 1790 (s, C=O), 1390—1510 (m, C=C), 700 (m, CH) cm^{-1}; MS (70 eV) m/z: 295 (M^+), 266, 252, 223, 180, 147, 120, 104, 77.

5-(4-Methoxyphenyl)-5-(3-bromophenyl)hydantoin (2j) UV (CH_3OH) λ_{max}: 232 nm; ^{1}H NMR (DMSO, 500 MHz) δ: 3.63 (s, 3H), 6.96—7.55 (m, 8H), 9.30 (s, NH), 11.16 (s, NH); ^{13}C NMR (DMSO, 125 MHz) δ: 55.61 (CH_3), 76.24 (C), 114.37 (2CH), 122.18 (C), 126.08 (CH), 128.21 (2CH), 129.65 (CH), 131.14 (CH), 131.37 (CH), 131.90 (C), 143.00 (C), 156.24 (C), 159.47 (C), 174.99 (C); IR (KBr) v: 3000, 3380 (s, NH), 1670, 1790 (s, C=O), 1380—1520 (m, C=C), 840 (m, CH) cm^{-1}; MS (70 eV) m/z: 360 (M^+), 331, 317, 288, 258, 210, 182, 180, 155, 134, 107, 104, 77.

Conclusion

In conclusion, to obtain a rapid, efficient and "green" synthesis of 5,5-diphenylhydantoin derivatives, ultrasound irradiation has been applied to the reaction mixtures containing symmetrical or unsymmetrical benzil derivatives and urea, which allowed us to achieve 5,5-diphenylhydantoin derivatives in a good yield and short time without any side product. This convenient procedure will allow a further increase of the diversity within the hydantoin family.

Acknowledgements

We are grateful to the University of Kashan for the partial support to this work.

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(E0909012 Ding, W.; Fan, Y.)

